# FACTORS REGULATING BLOOD PRESSURE

*Transactions of the Third Conference*
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# JOSIAH MACY, JR FOUNDATION CONFERENCE PROGRAM

FRANK FREMONT SMITH

With the accelerating rate at which new knowledge is accumulating and with the increasing recognition that nature is of one piece it becomes evident that the continued isolation of the several branches of science from one another is a serious obstacle to scientific progress

Nowhere in science is the need for combined operations more evident than in medicine Today to be effective medical research and practice must embrace data from all the disciplines including nuclear physics at one end of the spectrum and cultural anthropology at the other for advances in one field are frequently dependent upon knowledge derived from quite another discipline

Although the fertility of the multi discipline approach is thus recognized universities scientific societies and journals have not yet made adequate provision for channels of interdisciplinary communication

The Josiah Macy Jr Foundation therefore has endeavored to meet this need by bringing together for a series of two day annual conferences a small group of investigators representing in so far as possible all the branches of science which bear on a chosen problem These round table discussions of research experience concepts and plans are conducted in a friendly and informal atmosphere which promotes communication cross fertilization of ideas and cooperation The success of such an endeavor is dependent upon full participation of all members in the discussion Accordingly the attendance at any conference is limited to twenty five

Under the guidance of Dr Willard C Rappleye President of the Foundation since 1942 the Conference Program has been gradually expanded and enlarged until it now includes thirteen different groups which meet annually to discuss a wide variety of problems in the field of medicine and the closely related disciplines The Conference Program has become a major interest of the Foundation

In order to share with a wider group of investigators and students the essential quality of these conferences the informal nature and tempo of the discussions in so far as possible are preserved in the published transactions

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## *Third Conference on Factors Regulating Blood Pressure*

# INTRODUCTORY REMARKS

HARRY GOLDBLATT
*Institute for Medical Research Cedars of Lebanon Hospital*

Because of the late start which we are making this morning I have decided to make my introduction even briefer than usual for which I know you will be duly grateful

Those of you who have participated in previous Conferences know that when we were organizing this group we considered it desirable to get down immediately to fundamentals and discuss the subject of hemodynamics as it applies to the general circulation as well as to particular organs such as the kidney You know however that in the first two Conferences for various reasons this was not possible and that we resorted instead to the evaluation of previous progress and a mutual disclosure of our activities in the field of hypertension and vascular disease

These two past Conferences were valuable They certainly meant much to those who participated and judging from the popularity of the printed reports I would say that they also proved of considerable value to those who did not attend but who read the reports

Now at last at the Third Conference we have decided to make the topic of hemodynamics the subject of discussion I hope that this will also be the subject of future conferences because I do not feel that we can exhaust it in a single one

We are making another departure at this time by inviting the guests to be the contributors of most of the topics This should prove stimulating and of great value As you know and as Dr Frank Fremont Smith has emphasized we lay great stress on discussion and consider it the most important part of these Conferences We urge the guests also to participate

It seems to me to begin the conference with a discussion of the capillary circulation is appropriate and I am going to ask Dr Zweifach to be our first speaker

# BASIC MECHANISMS IN PERIPHERAL VASCULAR HOMEOSTASIS*

BENJAMIN W ZWEIFACH
*Cornell University Medical College*

The capillary bed represents a unique segment of the vascular system which although it is relatively independent of the remainder of the peripheral vascular apparatus is profoundly influenced by the state of the circulation in the arteries and veins on either side of it Passive changes in the capillary circulation result from fluctuations in the arterial blood pressure and in the degree of arteriolar constriction Active changes in blood flow are introduced by local mechanisms which regulate the blood flow to the tissues in accord with their varying nutritive demands Because of its relative inaccessibility the contribution of this portion of the vascular apparatus to the overall cardiovascular hemodynamics has not been subjected to a sufficiently critical analysis Discussions on cardiovascular hemodynamics usually refer to the peripheral circulation by a mathematical term which represents the so called peripheral resistance Actually the major resistance to blood flow lies in the arterioles The vessels which lie distal to the arterioles are then collectively referred to as the capillaries and are assigned a somewhat obscure role in the physiology of the vascular system as a whole It has been our thesis that this portion of the vascular system is intimately concerned with the initiation and perpetuation of a wide variety of circulatory disturbances including the hypertensive syndrome I would like to bring to your attention several basic mechanisms residing in the capillary bed which have been shown to play a significant role in the circulatory adjustments to both physiological and abnormal situations

From a functional viewpoint the peripheral vascular system consists of three major subdivisions After penetrating the tissue mass which they supply with blood the small arteries subdivide

*From the Department of Medicine The work described in this paper was supported by grants from the Josiah Macy Jr Foundation Eli Lilly and Company the Postley Hypertension Fund and the United States Public Health Service

to form relatively long narrow arterioles characterized by a single layer of thin muscle cells The arterial vessels up to this point serve as elastic conduits for distributing blood to the various organs Distal to the arterioles are the extreme ramifications of the arterial tree the so called capillary bed which represents the ultimate barrier across which tissue blood interchange occurs The venules draining the capillary bed join with one another to form small muscular veins which represent the initial components of the venous system of vessels The reactions of the peripheral blood vessels correspondingly fall into three main categories those concerned with the maintenance of blood pressure (arteries and arterioles) those concerned with the local regulation of blood flow in the tissues (terminal arterioles and capillaries) and those relating to the return of blood to the heart (muscular venules and veins) Being distal to the terminal arterioles the capillary vessels participate only indirectly in the regulation of the peripheral resistance and the blood pressure Their physiology is more directly concerned with the actual mechanics influencing the number of vessels to which the blood is distributed and the establishment of a balanced pressure relationship within the capillary system Acute changes in the circulation through the capillary bed in one tissue or organ usually do not affect the systemic blood pressure or blood flow in other regions Only in instances where a widespread change in the capillary circulation occurs simultaneously in a number of tissues or organs is the altered peripheral resistance of sufficient magnitude to affect the blood pressure or the systemic circulation However in chronic situations even minimal disturbances in the capillary circulation when maintained in a given direction for long periods of time will eventually produce systemic effects

The maintenance of local homeostasis resides in a delicate balance between local and systemic factors The systemic factors blood pressure and arteriolar resistance are integrated with one another by the sympathetic nervous system The local factors regulating blood flow not only influence the metarterioles precapillaries and venules but also the distal continuation of the arterioles immediately proximal to the capillary bed proper The arterioles thus constitute an intermediate zone which is under the influence of both local and systemic factors It is this portion of the peripheral vascular apparatus which will reflect changes in the capillary circulation and which in turn will be reflected in

the systemic blood pressure Other more subtle changes in the capillary circulation of a chronic nature will result in an imbalance in the effective circulating blood volume which in turn will have its effect on the systemic blood pressure It can be seen that local homeostasis cannot be maintained unless change in either the arterioles or in the capillary bed is compensated for by readjust ment in one or the other of the two systems In situations where the arterial blood pressure has been increased or decreased for long periods or where the venous pressure is elevated chronically or where the blood volume is progressively altered the capillary circulation can be maintained at normal effective levels only by some type of readjustment Conversely in situations where the capillary circulation is disturbed the arterial blood pressure the venous pressure and an adequately balanced water exchange be tween the blood and tissues can occur only by specific readjust ment of the arterioles leading to the capillary bed

Let us therefore begin our analysis of the factors regulating the capillary circulation by noting the manner in which the termi nal ramifications of the arterial tree are distributed in the tissues which they supply with blood The capillary bed has been depicted as arising from the repeated subdivision of the terminal arteries the haphazard interanastomosing of these channels and their join ing up with one another to build up the venous system of vessels This however has not been found to be the case The capillary bed is organized around a definite architectural pattern peculiarly suited to cope with the variations in the amount of blood it must distribute (2) The accompanying diagram (Figure 1) illustrates the structural pattern of the nutritive type of circulation Al though structural peculiarities because of the nature of the tissue will be found in different organs the type of structure illustrated is widely distributed in tissues including skin mesentery gut skeletal muscle and glands such as the pancreas In specialized organs such as the liver kidney and spleen structural makeup of the capillary circulation is considerably modified However cer tain characteristics such as the presence of precapillary sphincters and non contractile capillaries, are features which occur in all tis sues irrespective of their overall structural organization Figure 1 is taken from the mesentery where the capillary bed is seen in almost diagrammatic form The muscular arterioles inter inasto mose so that no single arteriolar vessel supplies a given capillary area Also several venules each terminating in a different large

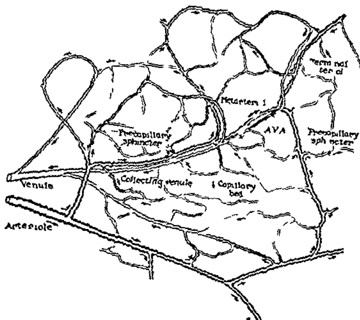



FIGURE 1 The camera lucida drawing of the capillary bed in the mesentery of the cat The vascular smooth muscle is indicated by a scalloped thickening of the vessel wall Several different types of preferential channels from arteriole to venule are seen The capillary network is supplied by two separate arterioles Note an A V A between a metarteriole and a collecting venule

*vein drain the area This makes it possible to maintain the capillary* circulation at relatively constant levels despite variations in *the arterial blood supply in any single feeding vessel*

The tissue requirements for blood vary considerably with the functional state of the organ and in tissues such as skeletal muscle *differences in the demands* between the resting and active state may be of the order of 10 and 15 to 1 For this reason the capillary *bed must be sufficiently elastic to allow for a marked expansion* of the number of vessels with an active circulation at *one period, and at a subsequent interval to permit only a small fraction of* the available vessels to function This *functional flexibility* is obtained by virtue of a *fundamental structural pattern of the capillary* bed, the *framework* of which is characteristic of almost all tissues (3) Most tissues display *alternating periods of greater* and lesser blood supply during which the blood becomes periodically confined to certain preferential centrally placed channels

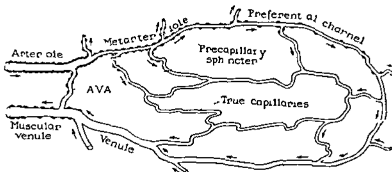



FIGURE 2 A schematic representation of the structural pattern of the capil lary bed The distribution of smooth muscle is indicated in the vessel wall

with the majority of the capillary vessels being devoid of an active blood flow The same thoroughfare channels are the only com ponents of the capillary bed which show spontaneous and readily recognizable changes in caliber and are the only vessels in the bed which undergo vasoconstriction with physiologic concentrations of epinephrine It is apparent that the vessels beyond the arterioles are not distributed haphazardly but consist of groups of functional units each organized around a centrally placed muscular channel from which capillary side branches are given off (Figure 2) The preferential channels are distinguished by having a discontinuous coat of thin branched poorly contractile muscle elements They are hence classified as muscular capillaries and are referred to as metarterioles The remainder of the capillary vessels are de nuded endothelial tubes which possess no contractile pericapillary elements and are termed non muscular or true capillaries The latter do not lie in the most direct path of flow from arterioles to venules and have only a sporadic and variable flow through them This arrangement permits the complete removal of the true capillaries from the active circulation without interfering with the flow through the more centrally placed preferential channel A significant feature of the capillary offshoot is the presence of one or two muscle cells about each of the outflowing side branches just as it leaves the parent vessel The term precapillary sphinc ter has been applied to this strategically placed junctional, mus cular portion of the capillary the state of contraction of which directly influences the blood flow into the capillary network

In addition to the preferential channels and their capillary branches there are also side branches which come directly off the arterioles These are muscular vessels which break up into numerous branches and rapidly lose their muscular coat Although such vessels resemble the preferential channels in their proximal portions no well defined channel can be traced through to the venous side Instead several capillary branches connect the vessel with the venous trunks

The venous system originates where several preferential channels join with one another to form what are called collecting venules This segment of the venous system has no muscular coat The collecting venules become wider after being joined by additional capillary vessels and acquire a heavy supporting coat of connective tissue together with irregularly spaced smooth muscle cells These muscular venules do not show any spontaneous rhythmic changes in caliber but do respond to vasoconstrictor substances such as epinephrine pitressin etc It is only after a long venule is formed with a well defined muscle layer that spontaneous vasomotor movements can be detected

In addition to the preferential channels shunts are provided whereby the blood may circumvent the network of capillary vessels to reach the venous channels In the normal circulation there are three routes for transmitting blood from the arteries to the veins

(1) The arteriovenous anastomosis (A V A ) has been found to be present not only in the skin but in almost every tissue which has been examined These structures are relatively short muscular shunts which bridge an artery with its contiguous vein The shunts are highly muscular in their arterial segment In the skin the A V A vessels are believed to have functional significance chiefly in the regulation of skin temperature However their universal *distribution indicates that they probably play a more important* role in the local regulation of peripheral blood flow Not only are such shunts seen between large arteries and veins between arterioles and venules but also (as is indicated in Figure 1) between metarterioles and nearby venules In the latter instances the shunts are only about 15 to 20 micra in diameter Their proximal portion resembles the precapillary sphincters in having a muscular coat only in the immediate segment where the vessel leaves the parent arteriole

(2) The arterioles are relatively long thin vessels which have numerous muscular side branches coming off almost at right angles Each of these side branches constitutes a metarteriolar capillary unit The distal continuation of the arteriole usually terminates by turning back on its course and joining with other capillaries to form a collecting venule This almost direct continuation of the arteriole to the venous circulation transmits a considerable volume of blood especially when the capillary beds supplied by its side branches are in an ischemic or resting state

(3) A third passageway occurs in the capillary bed proper through the preferential channels described above The preferential channel does not have uniform structural characteristics throughout its extent In the proximal portion the vessel possesses a discontinuous coat of smooth muscle As the vessels continue distally the smooth muscle coat becomes less abundant and finally is lost completely On close inspection this non muscular portion of the preferential channel can be differentiated from adjoining capillaries by the presence of a somewhat thicker supporting connective tissue coat In many instances it is difficult by mere inspection to differentiate between true capillaries and the distal portions of the preferential channels However after the preferential channel is joined by inflowing capillaries the vessel widens considerably and acquires a well defined perivascular connective tissue coat Little is known about the precise conditions which determine the extent of the circulation through each of the three above mentioned channels from arteries to veins

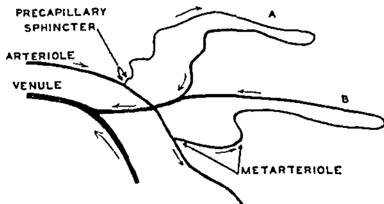



FIGURE 3 Diagram of the capillary bed in the nail bed of the human skin Note that each capillary loop has its own precapillary sphincter

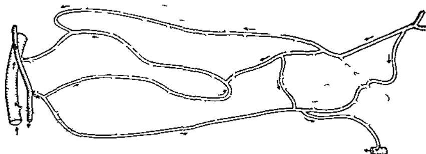


FIGURE 4 Camera lucida drawing of capillary bed in mesentery of dog True capillaries indicated by dotted lines

The relative number of capillary vessels of the metarteriolar type as compared with the number of non muscular true capillaries varies in different tissues according to the degree of fluctuations in activity which that tissue normally exhibits (10) For example in the skin the capillary loops which are observed in the nail bed of the human represent a direct connection between the metarteriole and the venule (Figure 3) Only infrequently do these vessels have a number of capillary branches In tissues such as the mesentery which maintain a relatively fixed level of activity there may be about two or three times as many true capillaries as preferential channels (Figure 4) In skeletal muscle which exhibits extreme fluctuations in nutritive demands during work the true capillaries are at least 8 to 10 times as numerous as the preferential channels Thus the preferential muscular vessels may be regarded as meeting the basal requirements of the tissue The true capillaries on the other hand constitute a reserve network which is brought into action only when there is an increased demand for the interchange of substances between the blood and tissues Under normal conditions variations in blood flow through the various components of the capillary bed are subservient to and regulated by the functional state of the tissues Under abnormal situations such as occur in various types of stress the increased activity of the sympathetic nervous system and/or the participation of humoral substances may alter the local regulation of blood flow

Emphasis should be placed on the fact that it is extremely difficult by simple inspection in living tissues to distinguish between the different types of capillary vessels The term capillary

is derived from "capilla" meaning hair like. With this as the only criterion all of the small blood vessels distal to the muscular arterioles would be classified as capillaries. Obviously caliber alone is not a distinguishing criterion. The peripheral vascular muscle cells are extremely thin and closely applied to the vessel surface making it difficult to distinguish them. Stress is therefore placed on the functional responses of the vessels as criteria for classification. A contractile response to either humoral or neurogenic stimuli is obtained in those vessels which have peripheral vascular muscle cells. Vessels which consist purely of endothelium are never oberved to undergo active vasoconstriction.

*Ogden*: When you emphasize those bends and twists near the sphincter and speak of them as diminishing the force of the blood the geometry looks like that which an engineer would put into a system to cut down on pulsations, and to convert pulsatile flow into direct flow. Has that possibility been considered in the teleology of it?

*Zweifach*: When one observes the capillary circulation under the microscope there is little or no indication of a pulsatile flow distal to the narrow arterioles. It is only under conditions of hyperemia and arteriolar dilatation that a pulsatile circulation is observed in the preferential channels. The terminal arterioles probably serve as a major factor in converting the flow to a continuous stream. The narrow precapillary sphincters tend to further damp out any pulsatile flow so that even under conditions of hyperemia, the blood circulating through the true capillaries exhibits no pulsatile characteristics. It is my impression that the sharp angle of branching combined with the tortuosity of the precapillaries serves to reduce sharply the hydrostatic pressure of the blood entering the capillary network. The rate of flow distal to these points is considerably slower than that in the parent vessel.

*Wakerlin*: These are pictures of rat mesentery?

*Zweifach*: Some are dog and some are rat.

*Fremont-Smith*: Would not Dr. Ogden's point hold that this tortuosity from a fluid dynamic consideration tended to diminish pulsations so that you would expect with a greater contraction of the precapillary sphincters a change from pulsatile flow to steady flow?

*Zweifach* The diameter of the terminal arterioles relative to that of the small arteries from which they stem is usually on the order of 1 to 3 or 4 This factor *per se* tends to convert the pulsatile flow in the arteries to an almost continuous one in the arterioles A damping effect is further enhanced by the passage of blood through the comparative long and narrow arterioles It is only under conditions of vasodilatation that a pulse is observed just proximal to the precapillaries In these instances the narrow sphincters completely abolish the pulse in the capillary tributaries distal to them

*Lamport* Can one observe changes in tortuosity with changes in flow through these vessels?

*Zweifach* Changes in the tortuosity of the vessels are frequently seen with changes in the flow through them With a marked increase in blood flow the tortuosity becomes less evident and frequently disappears This is especially apparent in many of the terminal arterioles and their precapillary branches

*Katz* I was brought up on the Rouget cell Where does it fit in your scheme?

*Zweifach* In many text books the capillaries are stated to be contractile by virtue of the presence of branched muscle cells in their walls the so called Rouget Cells We believe this to be a misconception based on fragmentary evidence The original investigators observed the presence of branched muscle like cells about vessels of capillary dimensions and assumed that such cells were distributed throughout the capillary bed Our own observations indicate that the vessels observed by these workers probably were the muscular preferential channels which I have discussed (9) A gradual transition from the typical spindle shaped smooth muscle cells in the arterioles to a thin branched muscle element occurs as the arterioles continue distally Thus in the metarterioles branched atypical muscle cells are observed Beyond this point however no contractile cells are present except for occasional muscular precapillary sphincters the true capillaries showing no evidence of changes in caliber attributable to pericapillary muscle cells

*Wakerlin* Has it not been considered that the Rouget cells found in poikilothermic animals are contractile but those found on the capillaries of mammalian species are not?

*Zweifach* The original description of the contractile pericapillary Rouget cell was made in amphibian forms Other investigators such as Vimtrup on the basis of histological data believed these cells also to be present in mammalian forms Several observers have noted that the endothelial vessels in the tadpole s tail appear to be contractile in response to direct stimulation We have made many thousands of observations on the circulation in tissues such as skin muscle mesentery gut and pancreas of mammals (rat cat rabbit guinea pig dog) and in the mesentery skeletal muscle and tongue of the frog In no instance where the endothelial wall was clearly visible did we find an active contraction of the endothelium either spontaneously or in response to various stimuli

*Katz* Do you mean that the narrowing is not uniform? You have pointed out that capillary tone is constant

*Zweifach* In the accompanying microphotographs (Figures 5 and 6) one can observe that the metarterioles when contracted have a varicose appearance The larger arteriolar vessels in which the muscle coat is almost continuous show a uniform narrowing of the vessel during contraction I have attempted to distinguish between those properties of the capillary vessels which are attributable to specific muscle elements and those which are the result of endothelial tone or elasticity Tonus is a property of the smooth muscle elements which maintains the cells in a state of partial contraction enabling them to counteract the dilating tendencies of the intravascular pressure Endothelial cells like all other living cells also possess the property of cell tone This property of the endothelial wall is analogous to elasticity of non cellular structures and permits it to resist distortion by the pressure within the vessel The response of muscular capillaries and non muscular vessels to stimuli differs greatly In vessels with muscle cells in their walls a constrictor stimulus brings about a rapid effect sufficiently pronounced to alter the blood flow through that structure On the other hand changes in caliber of the true capillaries as a consequence of endothelial tone or elasticity are far less evident and develop slowly The diameter of the capillaries under normal conditions is usually 2 to 3 micra greater than that of the red blood cells Thus the flow consists of a single column of red cells Should the diameter of the capillary diminish the red cells would have great difficulty in coursing through the vessel and

actually be distorted in such a circulation Although this condition is occasionally seen in certain structures such as skeletal muscle, where considerable variations in the extravascular pressure occur, there is no evidence for the existence of a generalized mechanism of this sort It is questionable whether changes in tone can actively reduce the caliber of the capillary during periods in which the blood is flowing through it A narrowing of the capillaries occurs only in the complete absence of an active circulation With an increase in arteriolar blood flow and opening of the precapillary sphincters the diameter of the narrowed capillary returns imme diately to its original tonic state

Under different experimental conditions it is possible to diminish capillary tone This occurs with noxious agents such as urethane or different poisons applied locally with micropipettes Under these conditions, the capillary vessels undergo considerable vasodilatation This is apparently the direct result of a loss in endothelial tone since there is no apparent change in intracapillary pressure

*Fremont Smith* You define the true capillaries as those with no muscle cells in their walls?

*Zweifach* Yes In one category we place the so called muscular capillaries which include the metarterioles and precapillaries in the other category are the non muscular true capillaries

*Fremont Smith* By definition you exclude from the true capil laries those vessels which possess the equivalent of a Rouget cell

*Zweifach* The distal continuations of the metarterioles pos sess cells similar to those described by Rouget These vessels respond to various constrictor and dilator influences and are considered to be muscular capillaries

*Katz* Does the endothelium of the true capillary thicken when it narrows?

*Zweifach* When the caliber of the capillary is diminished the endothelium can be seen to thicken In most instances the endo thelial nucleus actually bulges into the lumen of the vessel Occa sionally the inbulging of the endothelial nuclei when it occurs at a point of branching of the vessel may block the flow into the capillaries During periods of relative ischemia the collecting venules which are considerably larger (50 to 100 micra) narrow

to about one third of their original diameter under these conditions The preferential channels rarely show a complete absence of blood flow through them

*Katz* The older literature emphasized that widening of the capillary bed might be due to venular constriction You see stagnation of the blood with dilatation of previously narrow channels

*Zweifach* Obviously the state of the venous outflow is of importance in the circulation through the capillary bed It should be noted (Figure 1) that by virtue of the numerous interanastomoses the blood can leave the capillary bed by a number of different venular pathways The only point at which active venular constriction could occur would be in the large muscular venules which drain the blood from as many as 5 to 10 separate capillary beds When the collecting venule is mechanically compressed with a blunt microneedle the effect on the capillary circulation is a diversion of blood into other adjacent venules the blood appearing to take the path of least resistance When a somewhat larger venous channel is compressed so that none of the blood from the capillary bed has a free path of outflow there is a progressive accumulation of blood and a distention of the venous capillaries Under circumstances of partial venular constriction such as mentioned by Dr Katz the outflow of blood of the capillary bed would be considerably impaired It is my impression that should this circumstance continue for a long period of time a progressive accumulation of blood in the collecting venules would occur and in turn be reflected by a slowing of blood flow through the capillary bed There is no evidence that stagnant anoxia *per se* will lead to capillary dilatation Hence the appearance of capillary dilatation under conditions which lead also to venular constriction would have to be related to other factors which affect the tone of the capillaries It is possible that a general increase in the venous pressure would result in a slowing of the capillary bed flow and by interfering with the nourishment of the local tissues would produce a loss in capillary tone and a consequent dilatation of these vessels In perfusion studies in which the capillaries of the mesentery were observed under a microscope a progressive increase in the perfusion pressure did not result in a dilatation of the capillaries as long as the tone of these vessels was maintained With a sudden drastic increase in perfusion pressure an actual

rupture of the capillary vessels, especially those on the venous side developed

*Ogden* When you were speaking of certain circumstances in which the capillary endothelium has its elasticity changed does that mean under these circumstances that a capillary has a different diameter for the same pressure within it?

*Zweifach* There would appear to be present under normal circumstances factors which tend to stabilize the physico chemical state of the endothelial wall (4) With functional changes in the physiological range the endothelial tone does not appear to undergo significant variations A loss of tone or elasticity appears chiefly under abnormal or pathological situations It is my impression that changes in capillary tone do not play a significant part in distributing the blood flow through the capillary bed It is possible experimentally to produce changes in capillary tone either locally or systemically The change is a reversible one depending on the severity of the procedure As mentioned previously, stagnant anoxia *per se* does not result in a loss of endothelial tone In stress situations such as hemorrhage the capillary vessels may remain inactive for periods of several hours and following retransfusions show no evidence of an altered endothelial tone We have thus far been unable to find in chronic situations, such as hypertension an indication of a sustained increase in capillary tone with a resultant narrowing of the capillary vessels Whether the return from an atonic state to a tonic one in the capillaries should be considered as contractility is highly doubtful I believe for purposes of description at least that it would be best to consider contractility as being related to structures which respond rapidly to vasotropic or neurogenic factors and as a result produce changes in blood flow

*Katz* If you had constriction and a diminished egress of blood from one of your systems (either the true capillaries the preferential channels or the venules) would you get dilatation of any of the other systems? I am especially referring to the venous part of the system

*Zweifach* The outflow of blood from the capillary bed by way of the venous channels is influenced by a multiplicity of factors The most obvious factor is the effective hydrostatic pressure propelling the blood from the arterial vessels into the

capillaries and from there into the venules In widely dilated vascular beds a considerable proportion of the *vis a tergo* of the blood is dissipated before the venous side of the vascular tree is reached In such instances the flow in the collecting venules is slow and relatively inefficient No dilatation of the venules is observed In other situations which lead to vascular hyperemia the tone of the venules is frequently impaired and as a result the flow of blood through the capillary bed is markedly interfered with (12) At first this merely results in a diversion of increasing amounts of blood into the capillary side channels With time however the venules undergo considerable dilatation The capillaries themselves are affected only in extreme instances of venular dysfunction Mechanical interference with venous return from the capillary bed usually results in a by passing of most of the capillaries and a flow of blood only through the most direct pathways It is under such circumstances that the flow of blood through direct A V A vessels becomes important The muscular venules and small veins undergo slow periodic vasomotor changes which probably also aid in the return of blood from the tissues Venous valves are seen only in relatively large veins (300 to 400 micra) and would appear to play no direct role in the return of blood from the capillaries

*Katz* The capillary does not control the rate of flow through it? If it changes its tone which means changes in caliber for a given constant pressure then the capillary must determine the volume of blood flowing through it

*Zweifach* I have attempted to distinguish between mechanisms which are utilized by the organism to produce changes in capillary blood flow in response to rapidly changing requirements of the tissue and those which occur over long periods of time and in essence reflect the physiological status of the vascular tree in a particular area I have therefore enumerated on the one hand changes in blood flow which can be attributed to vasoconstriction and vasodilatation as a consequence of neurogenic or humoral constrictor and dilator factors On the other hand are the factors which maintain vascular tone and which may come into play in more chronic situations Under normal conditions the profound changes in blood flow which occur with fluctuations in functional activity of the tissues do not appear to involve alterations in either vascular or endothelial tone Changes in tone are more apt to be related to pathological phenomena For example changes in endo

thelial tone are reflected in the permeability characteristics of the endothelial wall This factor alone produces disturbances in capillary circulation over and above those introduced by hemodynamic factors such as blood pressure peripheral resistance etc Since endothelial tone is a reflection of the healthy state of the endothelial cell it is difficult to conceive how an increase in cell tone would occur The absence of normal endothelial tone in conjunction with the absence of blood flow through the capillary results in a narrowing of the vessel The presence of normal endothelial tone in conjunction with an active blood flow through the vessel, is reflected by the maintenance of the normal capillary caliber The loss of endothelial tone in the presence of normal intracapillary blood flow and pressure results in vasodilatation of the weakened endothelial wall The presence of abnormal or diminished endothelial tone, in conjunction with an increased capillary blood flow and pressure results in edema and extravasation of blood cells

*Schroeder* Do you see the phenomenon of plasma skimming very often that is constriction to the point where red cells can not pass the sphincter but plasma can? If so might that not account for these capillaries maintaining their volume?

*Zweifach* In order to clarify the feature of plasma skimming a fine suspension of carbon was injected into the blood stream so that the movement of plasma without cells could be visualized (13) Frequently a partial contraction of the precapillary sphincter occurs making it impossible for red cells to enter the capillaries Under such situations there is a slow inward trickle of plasma into these side channels These capillaries are referred to as inactive vessels in contrast to the capillaries with an active flow of blood through them In skeletal muscle the capillaries frequently run in the long axis of the muscle fibres When the muscle contracts the capillary is completely emptied of its contents by pressure from the outside As the muscle relaxes the capillaries do not remain narrowed but open up and fluid can be seen to move into them from both sides of the vessel

*Wakerlin* Have you ever tried mechanical stimulation of the capillaries of any of your preparations? I recall seeing motion pictures of the results of mechanical stimulation of the capillaries which appeared to show active contraction of the capillary wall These pictures were taken in the mesentery of a cat as I recall

*Zweifach* In a study carried out in 1934 we attempted to distinguish between contractile and non contractile elements in the capillary wall by using micromanipulative procedures Individual cells in the mesentery of a cat and rat were prodded with the tip of a fine microneedle When a smooth muscle cell in the wall of an arteriole or a precapillary sphincter is prodded a localized contraction ensues which produces a narrowing of the vessel at that point Mechanical stimulation of pericapillary cells about the true capillaries does not affect the diameter of the vessel The stimulated cells merely round up and move away from the capillary wall When an endothelial nucleus was prodded directly the endothelial cell tended to round up The nucleus frequently bulged into the vascular lumen and blocked the passage of blood past that point When constrictor agents were introduced locally with a micropipette a response was obtained in only those capillary vessels which possess smooth muscle elements The capillary endothelium remained unaffected Electric stimulation of the sympathetic nerve fibers in these tissues likewise produced only a contraction of the muscular capillaries but had no effect on purely endothelial structures We therefore concluded that under physiological conditions the only contractile components which were effective in changing the blood flow through the capillary bed were those in the walls of the arterioles metarterioles and precapillaries The endothelial vessels appeared to take no part in these rapid changes in blood flow

The structural details of the organization of the capillary bed are indicated in the accompanying photographs Note that the precapillaries are given off at an acute angle and frequently branch in a backward direction (Figure 5) Most of the precapillary branches especially those on the arterial side are coiled and tortuous This feature tends to break the force of the blood flow before it enters the capillary bed Branches which are given off further distally from the preferential channels have only poorly defined sphincters Finally offshoots of the preferential channel at the point where it is no longer muscular have no sphincteric control The capillaries which empty into the distal venous segment of the preferential channel gradually approach the venules in the direction of the blood flow and fuse with them

In the region of the precapillary sphincters the arrangement of the muscle cells together with the indentation of the endo




FIGURE 5 Photograph of a precapillary sphincter under low and high magnification The precapillary sphincter is in the contracted state Note the absence of flow in the capillary side branch

thelium at that point are such that a moderate contraction of the muscle elements has a pronounced effect on the blood flow past that point It would therefore appear that factors which influence the activity of these strategically placed muscle cells are of major importance in regulating the blood flow to the tissues and in influencing the exchange of fluid between the vascular system and the tissues

*Lamport* The microphotographs which you showed had axial streaming of red blood cells in the larger arterioles Do you also see axial streaming in experiments where very fine carbon granules are injected?

*Zweifach* Axial streaming is observed chiefly in the larger arteries and arterioles The terminal arterioles and capillaries are usually just wide enough to permit the passage of single red blood cells with a thin area of clear plasma at the periphery In perfusion experiments where no blood corpuscles are circulated and a fine suspension of carbon particles added to the perfusate axial streaming can be seen as far down as the metarterioles No such phenomenon could be detected in any of the true capillaries

A distinguishing feature which serves to make the terminal vascular bed relatively independent of the remainder of the circulation is its extreme responsiveness to humoral agents The metarterioles and precapillaries respond to concentrations of sub-

stances such as epinephrine or arterenol below those which affect the larger arterioles The muscular venules are the least reactive components of the capillary bed In addition, substances which arise locally in the tissue will directly influence the responsiveness of the capillary vessels in that region The effect of local tissue changes is sufficiently great to override more centrally mediated vasoconstrictor stimuli either of blood borne or neurogenic origin For example increased tissue activity such as occurs with increased temperature or following exercise by skeletal muscle or the production of a local irritation will prevent vasoconstriction from occurring in the capillary bed following direct nerve stimulation or sympathetic discharge Other factors such as pH local concentrations of electrolytes and metabolites similarly affect the responses of the terminal vascular bed to vasoconstrictor stimuli

In general two sets of forces serve to regulate the flow of blood through the small blood vessels Locally the vessels are influenced by the degree of cellular activity in the tissues and in order to insure adequate distribution of blood to different parts of the body the vessels are kept under the influence of centrally integrating systemic mechanisms The central regulation is introduced both by way of the sympathetic nervous system which acts primarily on the terminal arterioles and by way of the blood stream which contains principles influencing the tone and reactivity of the vascular smooth muscle cells The arterioles are primarily concerned with a central or systemic function the maintenance of blood pressure In addition they participate in a peripheral or local function the delivery and distribution of adequate amounts of blood to the tissues Under normal circumstances this produces no conflict However in certain instances the two functions are not mutually compatible Thus in stress situations such as occur following hemorrhage the blood pressure falls and the arterioles undergo vasoconstriction as a consequence of increased activity of the sympathetic nervous system (16) With the development of drastic hypotension the blood flow to the tissues is usually reduced below levels which are compatible with normal tissue function Local influences therefore come into play in an attempt to increase the blood flow in the tissue by dilating the precapillary sphincters When the hypotension is sufficiently prolonged the local dilatation will extend to the metarterioles and even to the terminal arterioles The terminal arterioles represent

ing a segment of the vascular system intermediate between the larger blood vessels and the terminal vascular bed are thus faced with conflicting stimuli tending both to constrict and to dilate the vessel Ultimate control resides in the tissue mechanisms by virtue of their direct effect on the smooth muscle cells Thus under con ditions of local dilatation the ability of the vascular smooth muscle to respond to stimuli is progressively impaired until even direct prodding of the muscle cells with microneedles does not elicit a constrictor response These local effects are readily reversible and within 10 to 15 minutes after the onset of a normal or resting state of tissue activity the responsiveness of the muscular vessels has returned

The term vasomotion has been used to refer to a periodic type of vasomotor activity observed in the terminal vascular bed (15) In the mesentery the circulation is characterized by alter nating periods of greater or lesser blood supply during which the blood becomes periodically restricted to the more centrally located metarterioles (preferential channels) while the majority of capil laries are devoid of an active flow of blood (Figure 6 A B) These fluctuations in blood flow were found to be related to an irregularly recurrent series of partial contractions and relaxations of the metarterioles and precapillary sphincters at intervals varying from 30 seconds to as long as 3 minutes This intermittent activity which has been termed vasomotion does not appear to be related to the vasomotor caliber changes of the larger arteries or arterioles The non muscular collecting venules show prolonged periods of partial narrowing followed by an equally long period of partial dilatation These changes occur very gradually over a period of 20 to 30 minutes and are impossible to detect except by means of time lapse motion picture photography There would appear to be no direct correlation between the vasomotor activity of either the arterioles the capillary bed or the muscular venules Under condi tions which produce local vasodilatation the vasomotion of the venules is the first to be affected that of the capillary bed under goes a more progressive impairment while that of the larger arterioles does not appear to be affected

Variations in vasomotion are of two sorts (a) alterations in the rate of the intermittent caliber changes and (b) alterations in the relative duration of the constrictor and dilator phases of the cycle With augmented vasomotion the frequency of the

FIGURE 6 Photographs of circulation in mesoappendix of rat during two phases of the vasomotion cycle (a) Vasoconstrictor phase the metarteriole is partially contracted Note its varicose appearance The precapillaries are closed Capillary side branches are empty but open. No change in their diameter occurs during cycle (b) Vasodilator phase the metarteriole and precapillaries open overall flow through capillary bed.

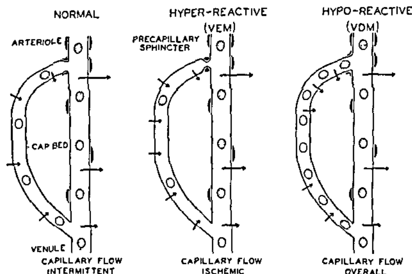



FIGURE 7 Diagram of fluid exchange between blood and tissues The number of stippled cells in the side branch indicate the number of open capillary channels The arrows indicate the preponderance of fluid movement the length of the arrow giving an approximation of the magnitude of fluid movement in comparison to the other capillary vessels

periodic contraction/relaxation cycle is increased with the constrictor phase becoming increasingly prominent With a depressed or impaired vasomotion the number of cycles are diminished and the dilator phase becomes progressively predominant The significance of disturbances in this function can be readily appreciated by noting its effect on the exchange of fluid between the blood and tissues (Figure 7) The Starling hypothesis considers the difference between the hydrostatic and the colloidal osmotic pressures as the effective force which is concerned with the movement of fluids between the blood and the tissue spaces The concept of vasomotion has further implications in this regard First with augmented vasomotion and closure of the precapillary sphincters an active flow of blood is present in relatively few capillaries These inactive capillaries will therefore have a comparatively low hydrostatic pressure *This makes available for inward filtration a large* number of capillary vessels The total surface area available for inward filtration is therefore in excess of that across which outward filtration occurs Such a situation favors hemodilution of the blood and this type of increased vasomotion is precisely what is

observed in the omentum following hemorrhage during the initial period when hemodilution takes place In contrast with a depressed vasomotion almost all of the available capillaries have an active flow of blood through them and are thereby exposed to the hydrostatic pressure corresponding to the blood pressure in that part of the system Under these conditions the surface area available for outward filtration is in excess of that for inward filtration This combination of circumstances brings about an increased flow of lymph in the terminal lymphatics which can be seen In conditions where impaired vasomotion is accompanied by dilatation of the arterioles edema develops rapidly A second consequence of vasomotion with respect to fluid exchange is the relative duration of the constrictor and dilator phases of the cycle Under certain circumstances the constrictor phase is relatively long and is followed by a short dilator phase This type of activity favors tissue dehydration In other situations the duration of the dilator phase of the cycle is abnormally long with respect to the short constrictor phase This situation favors tissue hydration

*Bazett* Do you mean that such constriction involves both the arterial and the venous sides? If both were comparably involved there would be no change in capillary pressure

*Zweifach* The vasomotor activity of the capillary bed is much more rapid than that occurring either on the large arterioles or in the muscular venules I have been unable to detect either a synchronous or a compensatory type of change relating the activity of the different vascular subdivisions to one another Such an interrelationship may possibly be of significance in chronic situations Most of the studies which I have described represent of necessity changes in vasomotion which occur under acute experimental conditions

*Goldblatt* Does the distal portion of the arteriole undergo vasomotion?

*Zweifach* It is difficult to draw a hard and fast line separating the arterial tree from the capillary bed There is of course an intermediate segment between the two This segment begins with one of the branches of the large arterioles which can be considered as a terminal arteriole As this vessel continues distally its muscular coat becomes thinner and less compact Side branches are given off which form capillaries Direct extensions and sub

divisions of the vessel also participate in the formation of the capillary bed as previously described One can however continue to follow the original arteriole into the capillary bed proper until the vessel loses its muscular investment The vasomotor cycle involves the precapillaries the muscular portion of the arteriolar tree within the capillary bed and a variable portion of the parent arteriole itself

*Stead* What evidence have you for pressure changes in the different vascular components of the capillary bed?

*Zweifach* Presumably little change in hydrostatic pressure occurs in the preferential channel The most pronounced changes in pressure would appear to occur in the side branches which are cut off from the active circulation by narrowing or closure of the precapillary sphincters Unfortunately we have no pressure measurements in the different capillaries during the various phases of the vasomotor cycle I have inferred however from the visible absence of blood flow that the hydrostatic pressure in these inactive capillaries must be comparatively low relative to the intravascular pressure during periods of active circulation through them There are obviously many other factors which should be taken into consideration such as tissue pressure state of the venous outflow and chemical nature of the local tissue environment

*Page* Is the vasomotion under separate chemical control?

*Zweifach* We have only meager knowledge concerning the factors which regulate peripheral vasomotion When the tissue under observation is denervated vasomotion ceases abruptly in the dilator phase of the cycle However within several hours the vessels begin to regain their original state of tonic contraction and for example in the vessels of the rabbit ear within 48 hours a slow periodic sequence of vasomotor changes can be seen in the precapillary sphincters We therefore have to assume that vasomotion is influenced both by nervous and humoral factors Vasomotion can be augmented by the administration of vasotonic agents such as pitressin or angiotonin Local warming of the tissue will bring about a slowing and finally cessation of vasomotion Cooling of the tissue affects chiefly the terminal arterioles which become considerably narrowed The vasomotion in the capillary bed is somewhat slowed but is still present

*Wakerlin* Is there any evidence for the existence of capillo motor fibers?

*Zweifach* The evidence for the precise innervation of the terminal vascular bed is inconclusive (11) Histological staining of fixed tissues by either gold or silver impregnation reveals only an incomplete distribution of nerves to the muscular components of the capillary bed Many of the precapillaries have no contiguous nerve strands about them Whether non muscular vessels such as the true capillaries are innervated is extremely doubtful There are descriptions in the literature of delicate meshwork of nerves surrounding all of the capillary vessels The nervous origin of these delicate fibers is not well substantiated Vital staining of the tissue with methylene blue likewise reveals delicate nerve fibers surrounding the terminal arterioles the metarterioles and some of the precapillaries Not all of the smooth muscle cells in these muscular vessels receive direct innervation Nerve fibers are not regularly seen about the capillary vessels except in instances where the nerve may have accompanied a capillary channel during its growth and extension into the tissue Physiological evidence regarding innervation of the capillary bed was obtained by observing the circulation in experiments where a discharge of the sympathetic nervous system was brought about through a stimulus such as asphyxia Asphyxia produces a systemic pressor effect and a widespread vasoconstriction In the capillary bed only the arterioles the metarterioles and a few of the precapillary sphincters are affected by such a discharge No constriction of the distal portion of the preferential channel nor of any of the true capillaries was seen The muscular venules undergo a partial narrowing On the basis of the above evidence we can conclude that the terminal vascular bed receives direct motor innervation to those vessels which have typical smooth muscle in their walls In the case of some of the precapillary sphincters and the distal portions of the metarterioles where the smooth muscle elements are atypical and branched there would appear to be no direct innervation These muscle cells however do respond to humoral substances The true capillaries do not appear to have sympathetic innervation Whether the capillary bed is under the influence of sensory nerve fibers remains open to question The evidence of Fulton and Lutz has been interpreted by them to indicate that vasodilator fibers are present in the capillary bed of the frog s tongue

It is interesting to follow the effects of sympathectomy on the capillary bed The denervated vessels become highly reactive to blood borne agents both vasoconstrictors and vasodilators For example, in the dog omentum the vessels under normal conditions respond to the topical application of one part in eight to one part in ten million of epinephrine Following dorsolumbar sympathectomy, the vessels in as little as 2 to 3 days respond to concentrations of epinephrine as low as one part in two hundred million This augmented reactivity falls off somewhat but is still present at least 4 to 5 months after sympathectomy

*Fremont Smith* May I add a word on the innervation of the arterioles of the human skin? It is well known that these are under sympathetic control and that after sympathectomy there is sustained vasodilatation and failure to constrict in response to emotional stimuli such as fear and anger to exposure to cold and to the vasoconstrictor phase of fever In 1928 29 at the Boston City Hospital we made observations on the nail bed capillaries in patients receiving typhoid vaccine intravenously and therapeutic injections of malaria organisms (Fremont Smith F Morrison L R, and Makepeace A W *J Clin Investigation 7, 489 1929*) During the onset of the chill phase but particularly as the fever reached its height and vasoconstriction was succeeded by vasodilatation it was evident that the flow through each capillary loop was under separate nervous control We observed repeatedly complete independence as far as flow was concerned, in adjacent capillaries For instance the flow in three adjacent capillaries might be at a standstill as the result of vasoconstriction then the blood in any one of the capillaries might flow rapidly while the flow in the other two remained at a standstill If the sympathetic innervation were limited to larger arterioles which controlled two or more capillary loops one would expect the flow to be similar in all the loops fed by such arterioles In view of the fact however that each loop behaved quite independently of the others in regard to flow it seemed clear that the sympathetic innervation must reach the terminal arterioles which in the skin feed a single capillary loop Our conclusions were that the terminal arterioles of the skin were individually innervated by the sympathetic nervous system and could be individually constricted at least in the conditions of fever studied

*Zweifach* It is my impression that the capillary loops seen in the nail bed of the human skin are direct offshoots of the termi

nal arterioles These vessels therefore would have a precapillary sphincter at their point of junction with the parent vessel Such sphincters are likely to receive direct innervation from the sympathetic nervous system This would explain the opening and closure of these vessels in response to sympathetic stimulation The independent activity of two adjacent capillary loops is a common observation in many tissues In the mesentery for example one arteriole may be in the constrictor phase of its cycle while the adjacent arteriole is undergoing dilatation The vasomotion of the precapillaries is even more unpredictable

*Fremont Smith* In this instance you would not expect vasoconstriction to be abolished by nerve section because it is under humoral control The point I am making is that it is abolished in the skin when the sympathetic fibers are cut

*Zweifach* As previously mentioned the phenomenon of vasomotion cannot be attributed to any single factor Following sympathectomy in the human not only is there a direct effect on the capillary loops which are being observed but the parent arterioles undergo vasodilatation There is some evidence from older perfusion experiments in animals that vasomotion of the precapillaries is in part related to changes in the intravascular pressure Thus as the pressure is lowered the constrictor phase of the vasomotion is accelerated and vice versa In the sympathectomized patient the precapillaries are under the influence of increased blood flow as a result of dilatation of the arterioles The increased circulation may serve as a factor inhibiting vasomotion of the precapillary sphincters

*Katz* Isn t it possible that nervous stimulation higher up may release humoral material which is not eliminated and can act more peripherally?

*Zweifach* There is a possibility that humoral principles liberated at the nerve endings surrounding the arterioles may be released into the blood stream and affect the response of the muscle cells distal to that point I would like to mention an observation which may be relevant to this feature Often the arterioles are connected directly with muscular venules by shunts Stimulation of the sympathetic nervous system produces a vasoconstriction of the arterial portion of this shunt the distal segment apparently having little or no muscle Concomitant with the constriction of the arterial portion of the shunt the venule which it joins under

goes constriction for a considerable distance down stream No constriction occurs in the portion of the venule proximal to the point at which the blood from the a v shunt enters This observation may indicate the release of some substances into the blood stream by the nervous system in conjunction with the vasoconstriction which is then carried by the blood stream to the venule and affecting its caliber

*Schroeder* If many of the vessels are not in phase it is difficult to explain the periodic variations that one finds for example in the fingers These fluctuations in volume are not apparently correlated with changes in blood pressure

*Zweifach* There would appear to be no direct relationship between fluctuations in the centrally recorded blood pressure and in the vasomotion of the peripheral blood vessels The changes in volume of the finger as recorded by electrical plethysmographic means show a number of different periodic features which have been interpreted as representing vasomotion in different parts of the vascular tree

*Schroeder* The long variations occurring at intervals of 30 seconds or more described by Burch and Cohn are not the result of changes of systemic arterial pressure

*Fremont Smith* In connection with Dr Schroeder s question, are there not vascular changes in the larger arteries which are independent of the peripheral vasomotion? The plethysmograph changes to which Dr Schroeder is referring I think are related more to changes in the vasomotor side in the larger arteries

*Schroeder* More of the volume however would be in the capillary bed or in the arteriovenous anastomosis

*Bazett* Isn t it true that you have multiple controls? There is no doubt that constriction of veins in the human skin and probably also in animals is a reflex matter you can get constriction of veins in one arm if the other arm is immersed in cold water Yet in recent work by J Pappenheimer the superficial vessels including the veins are found to contract if an excised leg is perfused with cooled blood There must therefore be at least two mechanisms present one reflex and the other dependent on direct reactions to temperature

*Zweifach* I would like to continue with a presentation of photographs indicating changes in the capillary circulation which

occur with different phases of vasomotion The pronounced effects on capillary blood flow which result from alterations in the pre capillary sphincters alone point to the importance of this vascular component in regulating the blood flow to the tissues

*Grollman* I feel that you are underestimating the importance of arterial tone as well as venular tone When you state that the manner of branching in the capillary bed to a large extent influ ences the distribution of blood in that area I agree wholeheartedly You also state that vasomotion in the so called preferential chan nels is a primary determinant of blood flow Perhaps as Dr Bazett said the flow is also dependent on other factors

*Zweifach* One cannot categorically isolate any portion of the vascular tree and treat it independently of the remainder This is especially true for a closed system such as the vascular tree For purposes of discussion an attempt to analyze the influence of specific factors makes it necessary to consider them singly without direct reference to other factors With regard to the point under discussion it should be realized that within a certain range the terminal vascular bed is a discrete functional unit Within this category it regulates the blood flow through the capillary bed in response to the demands of the surrounding tissue The blood flow will of necessity also depend upon the systemic blood pressure the tone of the arterioles and venules the viscosity of the blood etc These constitute modifying circumstances which under specific conditions may be magnified so as to constitute a major factor in peripheral hemodynamics However under normal conditions these factors remain relatively stable and the local distribution of blood appears to be solely the responsibility of the humoral and neuro genic factors which act on the metarterioles and precapillaries Although the local distribution of blood is regulated by local fac tors changes in the vascular tree proximal to this point must of course influence the blood flow in the terminal vascular bed How ever what is not clearly recognized is the fact that changes in the terminal vascular bed will also affect in a retrograde manner the arteriolar vessels proximal to them

*Fremont Smith* What you are saying if I may try to para phrase it is that in any particular area at any given time the major control of blood flow into the capillary bed is primarily determined by the activity of the precapillary sphincters This

does not contradict Dr Grollman's statement either What happens proximally and distally also influences this

*Zweifach* The tone of the arterioles proximal to and feeding into the capillary bed can be influenced by the activity of the vessels distal to them An example of this can be seen in experiments which have been used as evidence for the existence of an axon reflex It is possible by breaking off in the tissue a micropipette containing an irritant to produce a dilatation of the arteriole feeding this vascular bed Despite the fact that the locus of irritation is not physically contiguous with the feeding arteriole and is situated at least several thousand micra from the vessel, an arteriolar dilatation appears within 30 to 60 seconds The rapidity with which this response develops and the physical separation of the irritated area from the arteriolar vessel would seem to rule out the possibility that the reaction was the result of the diffusion of substances from the damaged tissue to the affected vessel A possible explanation is that a reflex arc is set into play which travels back along the sensory nerve fibers in the tissue and returns by way of the motor fibers to the terminal arterioles to produce a dilatation of these vessels

*Fremont Smith* May I suggest that substances diffuse into the bloodstream and are carried by the blood flow to the veins where possibly diffusion out of the vein occurs Also the possibility exists that there is a direct communication between the nerves in the veins and the contiguous arterioles

*Zweifach* The innervation of the capillary bed has been discussed in detail previously I have indicated that the retrograde effect on the arterioles produced by activity in the capillary bed probably develops by way of a reflex mechanism There is no direct evidence to indicate the path which such a reflex traverses No well defined sensory nerve endings have been demonstrated in the capillary bed Despite this no other visible explanation would appear to explain the effects produced by the deposition in the tissue of an irritant with a micropipette Perhaps if I were to explain the experiment in detail it would help to make clear the precise type of response which develops A small amount of glacial acetic acid is mixed with olive oil A microdrop about 8 to 10 micra in diameter of this mixture is then deposited in the connective tissue between the capillary branches The drop is usually at least 100 to 200 micra from the nearest capillary vessel The arteriole

feeding this vascular bed is usually several millimeters removed from the microdrop The irritant diffuses slowly and within 20 to 30 seconds produces a marked dilatation of the immediately adjacent capillaries At the end of about 45 to 60 seconds some of the capillaries still further removed (200 to 300 micra away) and precapillary sphincters in this range undergo dilatation Then within 15 to 20 seconds a marked dilatation of the feeding arteriole occurs flushing the entire area with blood It should be kept in mind that the extra cellular spaces are filled by a gel and not by a fluid The diffusion of substances through such a matrix occurs more slowly than would be the case if the extracellular matrix were liquid On the basis of this evidence I find it difficult to explain the type of reaction which develops purely on the basis of diffusion The explanation offered by Dr Fremont Smith regarding the uptake of material and its subsequent outward diffusion along the veins cannot be answered on the basis of present experimental data

*Grimson* Was the type of response altered by parasympathetic drugs?

*Zweifach* We did not carry out any experiments using such substances

*Dexter* I would like to challenge your statement regarding diffusion because the rate of diffusion can be so extraordinarily fast Are you using dyes with the same general molecular weight as the stimulating substance you are applying? I would just like to be convinced on this point

*Zweifach* The rate of diffusion of substances through the tissue spaces can be approximated by noting the manner in which dyes are spread through the tissues (14) Dyes of relatively small molecular size are used A small microdrop of the dye is deposited in the spaces between the capillaries The movement of the colored dye occurs evenly and rapidly moving across an area of about 100 micra in 20 seconds As the dye approaches the capillaries it spreads out in both directions along the long axis of the vessel The dye rarely traverses beyond the second or third capillary barrier that it meets and never has been observed to reach the origin of the arterioles Another type of experiment which may throw light on this point deals with the direct effects of locally deposited irritants Thus a microdrop containing an irritant can be deposited at different distances from the vessel wall and the time

noted for a vasodilatation to occur It was found that the diffusion times for vasodilator substances from the irritated region closely approximated those noted for dyes to diffuse across similar distances When larger molecular aggregates such as Evans blue or albumin stained with Evans blue, are deposited with a micropipette the diffusion time is considerably greater than that observed with similar molecular aggregates, such as phenol red or vital red

*Stead* Do vasodilator drugs diffuse at a comparable rate to epinephrine?

*Zweifach* Vasodilator substances such as acetylcholine or histamine were found to diffuse through the interstitial tissue matrix in a similar fashion to that observed with other substances such as epinephrine

*Bywaters* Did not Sir Thomas Lewis believe that this type of vascular reaction could be attributed to an axon reflex? Have you made any observations on sympathectomized areas?

*Zweifach* The experiments described above using the micro manipulative technique would appear to be similar to those described by Lewis in the vessels of the skin Lewis assumed that the evidence favored an antidromic type of pathway via the peripheral sympathetic nerves We have not made any observations on completely denervated regions

*Katz* May I offer a suggestion? Lewis in his experiments sectioned sensory nerves and produced degeneration and disappearance of this effect Wouldn t that kind of experiment give you your answer?

*Grimson* In the splanchnic area sensory nerves or visceral afferents travel along with the motor nerves or efferents through the splanchnic trunks Both would be interrupted by sympathectomy

*Zweifach* I would like to show photographs illustrating the type of change which occurs following the local injection of a vasodilator drug such as histamine Histamine is one of the agents which produces a marked increase in blood flow through the terminal vascular bed When applied locally by means of a micropipette, a differentiation between its direct effects on the different vascular components can be noted No direct effect on the true capillaries is seen When applied adjacent to the precapillary sphincters a pronounced dilatation of these structures occurs resulting in an




FIGURE 8 The effect of histamine injected locally into the tissue near the precapillary sphincter (A) The sphincter and its parent metarteriole are partially contracted (B) Note the dilatation of both vessels two minutes after the local injection of 1 10 000 of histamine phosphate

increased blood flow through the capillary network (Figure 8 A B) Under such conditions capillaries which previously were empty and partially narrowed open up under the influence of the increased blood flow With vasodilatation the precapillaries which are tortuous and partially coiled will tend to straighten out and lose many of the deformities originally present With respect to the possible relation of histamine to local dilatation and hyperemia under physiological or pathological conditions I would like to interject an observation on the effect of antihistaminic agents The intravenous injection of benadryl will abolish the local vasodilator action of histamine on the precapillaries and arterioles It does not however alter the vasodilator response to local irritation and the so called axon reflex continues to be elicited

*Lamport* Is it possible that a portion of what we call skimming is due to refraction at the edge of the vessel where the refractive index of the vessel wall may be slightly different producing a lens like effect so that that clear line we see is primarily refraction around the vessel and not true or at least complete axial streaming?

*Zweifach* True plasma skimming as defined by Krogh does occur when the precapillaries become partially narrowed In such a situation the opening of the precapillary sphincter is too narrow to permit red cells to enter the capillary side branches Evidence

for this was obtained by injecting a colored dye, such as Evans blue into the circulation The dye will rapidly enter the side channels despite the absence of corpuscular flow in these vessels Not only does the dye enter such capillaries but it also reaches the venous side of the bed within a short time

The phenomenon which Dr Lamport is referring to is of a somewhat different nature The rate of flow at the periphery of the blood stream and in the central core would appear to be different In experiments where carbon particles are introduced into the blood stream those particles which come to lie at the periphery of the stream within the vessel wall move more slowly than do those which are in the central axial stream

*Page* How do you tie in the work of Rous and his co workers on the gradient of permeability with your concepts?

*Zweifach* The work of Rous and co workers should be considered in relation to the schema which I have presented We have been able to confirm the existence of a similar gradient in the mesenteric circulation (14) When a number of dyes graded according to the size of the molecular aggregates, are introduced into the blood stream the larger sized dyes are retained by the capillaries on the arterial side of the bed and leave the blood stream only on the venous side of the circulation Hence it would appear that there is a gradient in porosity of the vessel wall as the preferential channel courses towards its venous side The outward movement of dyes on the venous side of the circulation does not necessarily indicate that there is no return of fluid into the capillary system along those points The two phenomena, viz outward diffusion of dye and inward diffusion of water probably occur independently of one another What must be taken into account here is the possibility that despite the lower hydrostatic pressure in this region the increased porosity of the capillary wall permits a greater outward filtration under a given head of pressure than would occur under similar circumstances through the arterial portions of the capillary bed

*Fremont Smith* Is the gradient of vascular permeability the fixed condition or does it vary with changes in the tissue environment?

*Zweifach* Apparently the anatomical gradient is dependent upon physiologic factors We have found it possible by blocking

the venous vessels to reverse the blood flow through the capillary bed The original arterial segment of the preferential channel now conveys venous blood Within 5 to 10 minutes the porosity of this segment increases until it approximates that of the venous vessels and permits large molecular dye aggregates to penetrate into the tissues We may therefore assume that the character of the gradient and its extent will vary under different conditions depending upon the venous character of the blood

*Fremont Smith* Will you indicate where a Venturi effect may occur at the point of inflow?

*Zweifach* A Venturi effect should be considered in evaluating the factors which influence the blood flow through the capillaries When one observes the movement of blood under the miscroscope it can be seen that the blood flow becomes slowed progressively as it courses from the precapillary region through the mid portion of the capillary network As the blood then approaches the venous end of the vessel it again begins to speed up and upon draining into the venule the blood actually appears to be sucked in by the stream flowing past the entrance orifice It has been assumed that the continuous rapid stream through the central channel may serve to create a region of relatively low pressure at the point where the incoming side branch joins the vessel As a result the blood stream will have an increased tendency to be drawn into the central channel from the side branch The state of the venous outflow from the capillary bed will in this manner influence the rate of inflow from the true capillaries

*Fremont Smith* While working with H S Forbes and H G Wolff in Stanley Cobb s laboratory at Harvard Medical School many years ago I have repeatedly observed this apparent Venturi effect in the cerebral veins as blood flows from a small venule to larger veins The flow is regularly smaller in the smaller vessels but as the corpuscles approach the opening into the larger vessel the speed can be seen to increase as if they were being sucked into the larger vein This seems to be the same phenomenon which you observed

*Ogden* It seems as if there is a region of sudden pressure change at the junction between the capillary and the venule

*Zweifach* Unfortunately there are no direct pressure measurements of this character

*Ogden* Dr Fremont Smith s observation of the blood corpuscles rushing past the point of capillary inflow suggests a region of high pressure

*Zweifach* It would be dangerous to generalize from observations on the rate of flow to pressure values in the capillary system. A sudden slowing or speeding of the flow in different regions may merely indicate a difference in pressure between the different parts of the capillary bed

*Lamport* When you suddenly see corpuscles speeding up it could be either the result of constriction of the vessel or increase in the amount of fluid and since at the venous end you have inpouring of fluid I think it is not unlikely that the increase in linear velocity that one sees is due to the return of fluid from the tissues there The Venturi effect I suspect is a small one I recall a computation in the glomerulus of the frog and it turned out to be extremely minute The kinetic energy there is very, very low. All the Venturi effect can do is to take kinetic energy and restore this potential energy namely pressure and convert it into kinetic energy thereby reducing the pressure So I feel that that explanation while it is glamorous is not right

*Fremont Smith* The change in rate of flow of the corpuscles or groups of corpuscles just as they enter the venule is very dramatic It is difficult to conceive of enough extra fluid coming in to account for this I am sure that the inflow of fluid must play some role Why the change of rate should be so sudden I don t know You would expect it to be gradual

*Zweifach* In our discussion today we were concerned with an analysis of the various local factors in peripheral homeostasis within the spheres of their specific function However one must also consider the interrelation between these peripheral mechanisms and the hemodynamics of the vascular system as a whole

The term homeostasis was introduced by Cannon (1) to stress the necessity for a tissue environment which remains stable despite a constant shifting in the multiplicity of nervous metabolic and humoral mechanisms concerned in the different bodily functions The primary function of the vascular system as a whole is to fulfill this basic requirement Any factor which either directly or indirectly interferes with the normal functioning of the tissue cells will disturb the local homeostasis and make necessary a readjustment of the local circulation to offset this imbalance

Peripheral vascular homeostasis is the resultant of two features a stable blood pressure and a blood flow specifically responsive to fluctuations in local nutritive demands of the tissues *Regulation of the blood pressure* is achieved primarily in that portion of the arterial tree which is proximal to the capillary bed viz the large arteries and the arterioles and is accomplished through the activity of the sympathetic nervous system which acts principally on the terminal arterioles and via angiotropic principles in the blood stream The *local regulation of blood flow* is achieved by changes in the activity of the arterioles metarterioles and precapillaries chiefly through the interplay of two sets of opposing vasoactive substances which influence the tone and reactivity of the perivascular muscle cells The arterioles therefore are concerned in both of these functions and represent a segment of the vascular tree intermediate between its two major subdivisions Because of this common denominator in both sets of reactions the two major functions cannot be dissociated from each other despite the fact that different mechanisms are involved in their operation

Under normal conditions with a fixed cardiac output and blood volume the blood pressure is dependent upon the total peripheral resistance a value determined essentially by the degree of arteriolar constriction Acute changes in the blood pressure of the large arterial trunks are activated by the sympathetic nervous system which in turn alters the degree of vasoconstriction in the arterioles Thus when the pressure falls the terminal arterioles undergo constriction and conversely when the arterial pressure becomes abnormally high arteriolar dilatation occurs It should be emphasized that these vascular adjustments are not the result of vasoconstriction or vasodilatation distal to the arterioles changes in the capillary circulation under these specific conditions occurring only as a consequence of the arteriolar caliber changes

Within the capillary bed proper the maintenance of normal peripheral circulatory adjustments is dependent upon the equilibrium between two oppositely acting sets of angiotropic principles The first has a restricting influence on the capacity of the peripheral vascular bed characterized by its potentiating or excitor effect on the reactivity of the terminal muscular components Included in this group of humoral principles are substances such as the adrenal cortical hormones pituitary hormones such as

pitressin hypertensin and the renal VEM principle etc The second related either to local cellular metabolic changes or to principles elaborated by organs such as skeletal muscle and liver serves to increase the amount of blood reaching the tissues by an inhibiting or depressing action on vascular reactivity (6 7)

The arterioles are directly influenced both by systemic and by local vascular mechanisms participating in homeostasis With the arterioles as a common denominator in both mechanisms it is inconceivable that changes in either systemic or local vascular behavior could occur without directly or indirectly influencing the other Each constriction of the arterioles not only sustains the blood pressure by increasing the peripheral resistance but also diminishes the blood flow through the capillary bed On the other hand a narrowing of the precapillary sphincters not only changes the blood flow locally but also the capacity of the vascular system as a whole Eventually the total peripheral resistance will be altered correspondingly

Numerous investigators have studied the effects of changes in blood pressure on the economy of the organism and on the hemo dynamics of the circulation However little attention has been paid to the other facet of the problem viz that changes in the mechanisms regulating the local distribution of blood will affect the mechanisms which are more directly concerned with the con trol of the blood pressure If this type of readjustment did not take place it would be impossible to achieve homeostasis Changes in local homeostatic factors are induced by disturbances in either the humoral or neurogenic controls or by development of local metabolic alterations necessitating a redistribution of blood Un less such disturbances are grossly abnormal they do not produce an acute change in either the blood pressure or in the effective circulating blood volume Under normal conditions there is a delicate balance between the amount of blood in active circulation and the capacity of the peripheral vascular tree Changes in the factors influencing the local circulation through the terminal vas cular bed when acting chronically over a prolonged period of time will bring about a change in the capacity of the vascular tree and will gradually set up an increased or decreased blood flow to the area by influencing reflexly the arterioles proximal to them Such an interrelationship is readily apparent from an analysis of the triple response described by Lewis (5) in the terminal vascular bed of the skin and other organs A region which is stroked

mechanically undergoes an initial blanching followed by a pronounced local vasodilatation Surrounding this hyperemic reddened area is a pale area In microscopic studies we have found that this pale area corresponds to a narrowing of the arterioles feeding the dilated capillary bed Thus the constriction of the arterioles protects the dilated capillaries by reducing the blood flow and the blood pressure within them In such a circumstance were the feeding arteriole maintained in a normal tonic state or dilated edema would develop rapidly in the dilated capillary bed It is the breakdown in these homeostatic mechanisms which results in obvious pathology

It is our hypothesis that a number of syndromes have as one of their basic features a functional or anatomical lesion in the terminal vascular bed which necessitates a readjustment of the arterioles feeding that area in order that a proper homeostatic balance be maintained Under certain conditions these changes may be confined to specific organs Such a response occurs in the circulation through different organs when they become active or in tissues such as skeletal muscle when they are stimulated in conditions of exercise In other situations a more widespread systemic type of disturbance in peripheral vascular homeostasis develops This is encountered in various stress situations such as trauma or hemorrhage or following general anesthesia

The participation of humoral factors in the vascular changes characteristic of conditions such as hypertension would involve primarily the terminal vascular bed the arterioles metarterioles and precapillaries whose components show the greatest response to such principles The reactivity of the terminal vascular bed is likewise influenced by the sympathetic nervous system which presumably through the axon reflex type of readjustment alters the caliber of the feeding arterioles in response to local tissue conditions In disease entities such as hypertension we may therefore have a series of vascular episodes which involve both humoral and neurogenic factors (8)

With the development of newer techniques for evaluating the responses of the peripheral vascular apparatus and our increasing knowledge of the specific metabolic processes related to vascular homeostasis a more direct approach on a fundamental level should be possible in a variety of disease conditions involving the peripheral vascular system

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*Goldblatt* As I intimated free discussion need not stop It may go right on after the presentation of the next topic

# A CONSIDERATION OF THE VENOUS CIRCULATION

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My point of view is similar to that of Dr Zweifach but my point of attack is different He has been talking about facts while I plan to safeguard myself by talking entirely about imaginary figures

In regard to the venous circulation there are only four statements on which we all appear to agree The first concerns the importance of the subject the second points out our appalling ignorance in regard to it the third is an agreement that veins have muscular coats and can constrict actively and the fourth states that the capacity of the venous system is very large as compared with the rest of the vascular bed

These we can review The existence of venous constriction needs no emphasis it is readily visible in superficial veins The work of Hooker (8) Fleisch (5) etc indicates that splanchnic veins constrict and take part in reflex vascular reactions

Physiologists are apt to stop there and say little more about the veins You will find little discussion of the subject in physiological texts not excluding sections that I have written The result is that students are apt to interpret our silence as indicating that the subject is unimportant rather than that we are ignorant I intend to discuss things beyond my knowledge hoping thus to stimulate discussion and to lead to the advancement of new ideas

I have attempted to make a balance sheet representing blood distribution on the approximate assumption that a man weighing 63 kilograms has a blood volume of some 5 2 liters (see Table I) This assumption is probably reasonably true for recent estimates made by dye injection carbon monoxide inhalation or radioactive phosphorus do not differ greatly from one another (4 11) The volume of blood in the large central veins heart pulmonary system and in the aorta and large arteries (to the femoral) is that

TABLE I

APPROXIMATE ESTIMATES OF BLOOD DISTRIBUTION IN THE VASCULAR BED OF A HYPOTHETICAL MAN 30 YEARS OF AGE WEIGHT 63 KG HEIGHT 178 CM BLOOD VOLUME ASSUMED = 5 2 LITERS

| Area | Vol in ml | Area | Vol in ml |
|---|---|---|---|
| Heart | 250 | Aorta | 100 |
| Pulmonary arteries | 400 | Systemic arteries | 450 |
| Pulmonary capillaries | 60 | Systemic capillaries | 300 |
| Saccular venules | 140 | Venules | 200 |
| Pulmonary veins | 700 | Systemic veins | 2050 |
| Total Pulmonary System | 1300 | Total Systemic Vessels | 3100 |
| and Heart | 250 | Unaccounted 550 | |
| | 1550 | (Probably extra blood in reservoirs of liver and spleen) | |

estimated from Hamilton s data (7) The volume of blood contained in the heart allows for considerable residual blood as described by Nylin (11) and is probably somewhat below its average value Ratios of the volumes of arteries capillaries and veins are derived from Schleier s data (16) except that the volume of the capillaries in the systemic vessels has been arbitrarily increased by some 220 ml since the capillaries in muscles are likely to exceed considerably those present in the digestive tract utilized for Schleier s calculations A possible check exists in that the figure originally calculated from these rash assumptions for the volume of the pulmonary capillaries agreed within 6 ml with that estimated by Roughton (15) on a basis of the rate of carbon monoxide absorption even though the figures were obtained quite independently The figure given in the table is an adjusted value reached by utilizing all available data The estimates do not add up to the total volume of the blood An additional 550 ml are assumed to be present in the liver and spleen, as is indicated in the table

Thus it would appear that the venous systems in the pulmonary and systemic vessels account for at least 3 liters out of the total volume of 5 2 liters

*Katz* The overall variable capacity of the hepatoportal system in man has been estimated to be about three liters Your figure for that is 550 cc

*Bazett* This figure represents only extra blood over and above that estimated for the whole systemic circulation The assumption made is that errors are likely to be particularly in evidence in calculations applied to these complex organs

Taking another side of the subject we may see what values must be given to the resistance to flow offered by the venous system (Table II) Resistances are usually expressed in C G S units (3) or in P P U (6) units I don t like either unit because I

TABLE II

RESISTANCE FOR RESTING SUBJECT WITH FLOW OF 5.8 LITERS PER MINUTE AT MEAN BLOOD PRESSURE OF 90 MM

$$\text{P P U} = \frac{90 - 0}{5800/\text{min}} = 0\,0155 \text{ units}$$

$$\text{C G S} = \frac{(9 \times 13\,6 \times 981 - 0}{97/\text{sec}} = 1\,230 \text{ units}$$

$$\text{R units} = \frac{90 - 0}{97/\text{sec}} = 0\,93 \text{ units}$$

Conversion of R units to P R U — divide by 60
to C G S — multiply by 1 332

consider them inconvenient If you have an individual with a rest ing blood flow of 5 8 liters per minute and a mean arterial pressure of 90 mm Hg the value calculated for resistance in P R U units is 0 0155 and in C G S units 1 230 (see Table II) Neither figure is easy either to remember or handle On the other hand if the ratio of pressure gradient to flow be calculated from pressures measured in mm of Hg (as in P P U calculations) and from flows measured in ml per second (as in C G S estimates) a ratio of 0 93 is obtained Such a unit for resistance is here termed an R unit It has the convenience that the resistance in the whole systemic circuit in a normal subject lying at rest approximates 1 and provides therefore a convenient standard All values given in the following discussion are consequently given in these units

*Goldblatt* Will you define P P U and C G S

*Bazett* P R U represents the ratio of a pressure gradient measured in mm Hg relative to a flow measured in ml per minute C G S units express the same ratio when the pressure is measured in dynes per square centimeter and the flow is measured in ml per second Thus the ratio may be considered $\frac{\text{dynes/cm}^2}{\text{cm}^3\text{/sec}}$ which transposed becomes dynes sec $\text{cm}^{-5}$ The value $\text{cm}^{-5}$ is apt to bewilder physicians The ratio is impressive in its method of presentation but is no more accurate than the simple ratio from which it is derived All of the ratios however expressed are in reality inaccurate They consider only the ratio of pressure energy to flow rather than that of the total free energy to flow No account is taken of kinetic energy which is considered always to be insignificant This is by no means always true Later I want to consider exercise in which kinetic energy cannot be excluded particularly in considering the pulmonary circulation Under such conditions in this circuit kinetic energy probably can sometimes account for half of the total energy To neglect its consideration here because it is insignificant in considering the work of the left ventricle at rest does physiology no great credit

*Lamport* Do you believe it is wrong to define the resistance of pressure flow ratio?

*Bazett* I think it is wrong It should be free energy that is considered To make the estimate of resistance correct the pressure gradient should be corrected by the pressure value of any other form of free energy which may be present originally and be dissipated I have not myself used such a correction because I do not know how to do it but we should admit our inaccuracies

*Fremont Smith* Wrong in what respect the terms or the kind of usage?

*Bazett* We may draw wrong deductions because we are assuming in such estimates of resistance that flow is always determined by the pressure gradient alone and this is often significantly untrue Kinetic energy is directional energy and it may be present in significant amounts particularly in the pulmonary system where pressure energy is low and in the systemic circuit in aortic regurgitation where peak velocities are high It cannot always be neglected

*Dexter* Would you explain how much difference in kinetic energy occurs as a result of exercise?

*Bazett* Pressure energy increases roughly proportionally to the flow kinetic energy as the square of this flow The latter forms therefore a greater proportion of the total as the rate of flow becomes higher Under normal resting conditions kinetic energy represents about 2 to 3 percent of the total energy in the pulmonary system the pressure energy is only about one fifth of that in the systemic the kinetic energy is approximately the same and consequently represents some 10 to 15 percent of the total If in exercise the flow is quadrupled the velocity energy is multi plied 16 times When the rate of flow is quadrupled the pressure energy is normally not greatly increased in either the systemic or pulmonary circuit since resistance is either actively or passively reduced Kinetic energy is enormously increased though its effec tiveness can be reduced by the development of turbulence

*Lamport* Do you mean that the index which you are looking for is one that will give the total amount of work being done on the circulation?

*Bazett* I think it would be preferable

*Lamport* It is important to define it

*Bazett* I would prefer to stay in our present position but also to recognize its defects

*Lamport* Pressure flow ratio is very useful We should not condemn the term only that it is wrong to use it as an index of work

*Bazett* I accept that We tend to generalize as though we represented the whole story when we do not

I want now to consider the relationship of resistance in the veins to the total resistance in any circuit This is represented in Table III Here the average capillary is considered to be that in which osmotic and hydrostatic forces balance even though the anatomical point of balance will not be the same under different sets of conditions However on such a definition we can divide the total resistance into precapillary (mainly arteriolar) and post capillary (mostly venule and venous) elements If the mean arterial pressure is assumed to be 90 mm as before average

TABLE III

RESISTANCE IN ARTERIAL AND VENOUS CIRCUITS IF MEAN PRESSURE AT CENTER OF CAPILLARY = 25 MM HG

Arterial Resistance $= R_a = \dfrac{90 - 25}{97} = 0.67$ R units

Capillary to Rt Auricle Resistance $= R = \dfrac{25 - 0}{97} = 0.26$ R units

Ratio R /R = 2.6

capillary pressure to be 25 mm and the pressure in the right auricle zero relative to atmospheric pressure then precapillary and postcapillary resistances are 0.67 and 0.26 R units as indicated in Table III The venous resistance is 1/2.6 of that of the arteriolar or 28 percent of the total resistance Venous resistance cannot have the negligible insignificant value which is commonly assumed

*Bradley* That would hold only for someone completely relaxed almost dead

*Katz* Does that not apply primarily to the venous-capillary to use an old fashioned term?

*Bazett* It may be the venule

*Lamport* I would like to point out that the same ratio is obtained even when the subject is not at rest

*Fremont Smith* You are taking pulmonary pressure as being zero?

*Bazett* I am leaving the pulmonary circulation temporarily out of the picture and confining attention to the systemic system of vessels I am assuming that right auricular pressure is equal to atmospheric pressure though it is certainly above intrathoracic pressure I think Dr Cournand would agree that the assumption is not far from the truth

*Cournand* Within 3 or 4 mm Hg

*Bazett* I want now to consider what must necessarily happen (at least approximately) during exercise This is indicated in

TABLE IV

EXERCISE

If cardiac output
increased from 5 8 to 17 4 liters/min
mean pressure from 90 to 120 mm Hg
rt auricular pressure decreased from 0 to −5 mm Hg
average capillary pressure remaining at 25 mm Hg

$$\text{Overall Resistance} = \frac{120 + 5}{291} = 0\ 43 \text{ P units}$$

$$\text{Arterial Resistance} = \frac{120 - 25}{291} = 0\ 33$$

$$\text{Venous Resistance} = \frac{25 + 5}{291} = 0\ 1$$

Ratio of P /P = 3 3

Table IV Here the cardiac output is assumed to increase from 5 8 to 17 4 liters per minute (i e 3 times) which is well within possible ranges Actually measurements on young normal individuals indicate that even with heavy work mean pressure does not rise greatly for diastolic pressure usually falls In the table mean pressure is assumed to rise only from a level of 90 to one of 120 mm Judged by experiments on dogs the right auricular pressure probably falls (10) This is indicated in the table Whether any fall is due to a relatively rapid emptying by the ventricle or whether it merely depends on a reduction of intrathoracic pressure is here immaterial One may assume that average capillary pressure in the body as a whole does not differ much from a 25 mm level at which osmotic balance occurs since a large fluid shift would be disadvantageous Capillary pressure might rise in the muscle capillaries and be associated with increased lymph flow but opposite changes might occur in other areas Pre and post capillary resistances are therefore calculated on a basis of an assumed unchanged level for capillary pressure Venous resistance is estimated as considerably lowered on an absolute basis and as constituting a somewhat lower proportion of the total resistance

(as might be expected in the presence of a muscular pump), but it still appears to be of the order of some 23 per cent of the total

Thus far the systemic circulation has been considered as a whole It is of interest now to attempt to divide it and to assign parts of the flow to different areas Here we come to a problem where I am certainly out of my depth, yet theoretical considerations prove enlightening In exercise, most of the circulation passes to the limb muscles whereas at rest a larger proportion goes to the kidney to the portal system including the liver and to the brain

Table V represents an attempt to assign blood flow to different areas in the hypothetical subject weighing 63 kilograms when he is at rest This is a tabulation produced for reproduction in later revision of Macleod s textbook For some of the data used I am indebted to Dr Bradley who supplied information on research work he was then carrying out Here one item can be stated with *certainty the total oxygen consumption of all the tissues can* rightly be assumed to total about 250 ml per minute The portal circulation is the largest at rest and may be considered to account for some 51 ml of this oxygen consumption The kidneys have the next largest flow but with an oxygen consumption of only about 14 ml per minute The brain and other nervous tissue have a flow of 12 5 ml /sec but have a large oxygen consumption Fairly good figures are now available for coronary flow which agree with those given in the table (which actually were estimated indirectly from dog experiments) Here the flow is low but the oxygen consumption high These four components account for $\frac{138}{250}$ (55 per cent) of the oxygen consumption and $\frac{61\ 8}{97}$ (63 percent) of the blood flow The 4th and 5th items of the table are somewhat doubtful That representing oxygen consumption of resting muscles is derived from Asmussen s data that representing blood flow in such muscles from estimates by Barcroft and Edholm The skin circulation is estimated from heat exchange and common values for the caloric loss per ml of blood flowing while the arteriovenous oxygen differences are based on analyses of venous blood from hand veins However rough these estimates may be they seem not to give serious errors for the arteriovenous oxygen difference of

TABLE V

TENTATIVE BALANCE SHEET OF RESTING REGIONAL BLOOD FLOW AND OXYGEN USAGE ASSUMED SUBJECT OF 1 8 M WEIGHING 63 KILOGRAMS AND WITH MEAN PRESSURE OF 90 MM HG

| | | Assumed mass tissue Kg | O /ml /min | *Flow* ml /sec | Resistance in R units | Assumed or observed A V O diff | Comments |
|---|---|---|---|---|---|---|---|
| 1 | Portal | 2 6 | 51 | 25 | 3 6 | 3 4 | |
| 2 | Kidney | 0 3 | 14 | 21 | 4 3 | 1 1 | Resistance extremely low for organ size |
| 3 | Brain and Spinal Cord | 1 4 | 46 | 12 5 | 7 2 | 6 2 | |
| 4 | Muscles | 31 | 50 | 14 | 6 4 | 6 0 | O usage Asmussen s data Blood Flow H Barcroft s data |
| 5 | Skin | 3 6 | 12 | 7 | 11 7 | 3 0 | |
| 6 | Heart Muscle | 0 3 | 27 | 3 3 | 27 | 13 5 | |
| 7 | Residue | 23 7 | 50 | 13 5 | 6 7 | 6 2 | Including thyroid etc and skeleton |
| | Total | 63 | 250 | 97 (5 8 liters/min ) | 0 93 | 4 3 | |

Superior V C flow estimated as 1 5 liters/min at A V diff of 5 8 = 87 ml O
Inferior V C flow 4 1 liters/min at A V diff of 3 3 = 136 ml O
*Coronary flow* *0 [illegible] lite s/min* at A V diff of 13 5 = 27 ml O

6 2 estimated from residual oxygen consumption and blood flow seems reasonable Probable compositions of superior or inferior caval blood estimated from the other values are given at the bottom of the table

In the table the resistance values of the various circuits for the assumed conditions are given It will be noted that those of the portal and renal vessels are very low that for the renal being exceedingly low when consideration is given to the size of the organs with a total mass of about 0 3 kilograms (With small organs the total number of vessels open must obviously be smaller, provided that other conditions do not vary The resistance therefore tends to vary inversely as the weight of the organ ) On the other hand the resistance of resting muscle with a flow of some 800 ml per minute to a mass of some 31 kilograms is surprisingly high for such a large mass of tissue

During exercise these conditions must change violently Kidney flow is reduced while I have assumed that the flow to the nervous system may either remain unchanged or rise proportionately to the increase in mean arterial pressure Flows must undoubtedly increase enormously in the skeletal muscles in the coronary circulation and in the supply to the skin (if the work is of long duration needing maintenance of a thermal steady state) In Table VI some attempt is made to estimate balances

The flow has been assumed as 17 4 liters per minute during the exercise 14 3 of these are supposed to supply the muscles and skin while the flow to the portal system is supposed to have been

TABLE VI

ASSUMED CHANGES IN REST TO EXERCISE IN CIRCULATION GENERAL AND LOCAL TO LIMBS AND PORTAL SYSTEM

| | Rest | Exercise | |
|---|---|---|---|
| Cardiac output | 5 8 | 17 4 | liters/minute |
| Flow to muscles and skin | 1 25 | 14 3 | liters/minute |
| Flow to portal system | 1 5 | 0 5 | liters/minute |
| Mean arterial pressure | 90 | 120 | mm Hg |
| Right auricular pressure | 0 | −5 | mm Hg |
| Mean capillary pressure muscles and skin | 25 | 30 | mm Hg |
| Mean capillary pressure mesentery and gut | 25 | 20 | mm Hg |

reduced from its resting 1 5 liters to 0 5 liters per minute Flow to the coronary system is not listed in the table but might be assumed as remaining about 34 percent of the total flow or as increased from 200 to 600 ml per minute The flows represented in Table V under 2 3 and 7 totaled at rest 2 8 liters/minute the bulk of this representing flow to the kidney and brain these are assumed to be reduced to 2 5 liters/minute with some increase in the flow to the brain and with reductions in other areas particularly the kidneys The average capillary pressure has been assumed to be raised somewhat in the active muscles where lymph formation is certainly increased and to be reduced somewhat in the intestinal vessels where water absorption is likely to occur Such changes are indicated in the table but the quantitative value of such changes if they exist is quite unknown and figures inserted in Table VI are entirely arbitrary

From such assumed figures theoretical resistances in the various circuits during exercise can be calculated (neglecting kinetic energy in such calculations even though it is probably not negligible) The values cannot be correct but it seems probable that they would indicate correctly the direction of change

Table VII indicates an enormous reduction in the overall systemic resistance during exercise This is certainly true The resistance of flow through the muscular vessels is reduced to about 12 percent of the resting value and this reduction is distributed

TABLE VII

ASSUMED CHANGES IN REST AND EXERCISE IN REGIONAL RESISTANCE

| | Rest | Exercise | Comments |
|---|---|---|---|
| Total Resistance | 0 93 | 0 43 | |
| Muscle and Skin Arterial Resistance | 3 1 | 0 37 | |
| Muscle and Skin Venous Resistance | 1.2 | 0 15 | Muscular pump |
| Ratio Muscle P /P | 2 6 | 2 5 | |
| Portal Arterial Resistance | 2 6 | 12 0 | |
| Portal Venous and Liver Resistance | 1 0 | 3 0 | Resp pump |
| Ratio Portal R /P | 2 6 | 4 0 | |

almost equally between the arterial and venous sections if the average capillary pressure in the muscles undergoes no greater change than that assumed The reduction in the venous resistance is no greater than that on the arteriolar side in spite of the functioning of a muscular pump In the absence of such a pump one must assume that the rise in capillary pressure would be considerable

If you assume as has been the case here that portal flow is reduced to 1/3 the resting value while the average capillary pressure in the mesenteric vessels has only been slightly reduced one has to assume that the venous resistance (or liver resistance) in the portal circuit has been greatly increased in spite of the concomitant greater activity of the respiratory pump which should lower this resistance How is this increase to be explained?

*Fremont Smith* Would you repeat those two alternatives?

*Bazett* You have either to assume that capillary pressure in the mesenteric vessels is greatly altered and by no means remains constant when the rate of flow alters or else you have to assume that capillary pressure is relatively constant and that venous resistance alters greatly just as does that on the arteriolar side Fluid resistances obey laws similar to those expressed for electrical currents in Ohm s law A change in resistance limited almost entirely to the arterioles and assumed to be accompanied by little change in capillary pressure or fluid exchange in the area supplied appears mathematically impossible without great changes in capillary pressure

*Ogden* What was the reason for saying that the portal pressure would be elevated?

*Bazett* The capillary pressure should be down at least to some extent It involves a larger gradient along the portal venous system *in proportion to the rate of flow*

*Ogden* Does this actually involve a pressure in the portal vein?

*Bazett* It does not matter The conclusion only involves the venous pressure gradient relative to the flow for the whole calculation refers only to venous resistance Nor is it possible to distinguish with the data available between resistances along the portal veins and resistance in the liver Particularly is this the

case when liver capillaries receive blood both from the hepatic artery and from the portal vein We have not even enough data to allow an intelligent guess

*Katz* It would be guessing even if we measured the portal venous pressure I don't know if it has been done during exercise

*Bazett* The difficulty would be to do it in man

The question arises how venous resistance could be regulated so that capillary pressure undergoes only small changes if we accept this as the more probable condition Krogh (9) emphasized that capillary pressure was maintained partly by mechanical increases in venous resistance resulting from partial collapse and consequent increase in frictional loss of free energy In the arm raised above the head capillary pressure could be reduced to 3 or 4 mm Hg but not lower Such results indicate considerable changes in capillary pressure partly counterbalanced by venous collapse On the other hand considerable evidence of active venous constriction in reflex responses also exists There can also be no doubt that changes in venous caliber whether actively or passively produced must be of great importance from their effects on vascular capacity

A valuable analysis of venous resistance in the perfused limbs of animals has been made by Pappenheimer and Soto Rivera (13) in which the conditions necessary to allow neither gain nor loss of weight in the limb were determined To adjust capillary pressures so that the isogravimetric state was attained venous pressures had to be balanced against those available on the arterial side It was found that a straight line resulted if the isogravimetric venous pressure was plotted against the corresponding rate of flow This implies that venous resistance was not altered by distension of the veins at different pressures provided that collapse of the veins was avoided as was the case in their experiments Regulation of venous resistance mechanically according to the pressure distending the vein appears only to function at the lower pressures when partial venous collapse develops

Possibly the perfusion experiments involve venous pressures and resistances outside the common range since the venous resistance in these experiments was usually only 1/10 of that in the arterioles and not approximately 1/3 as it appears to be when estimated from conditions likely to exist in man On the other

hand only part of the venous path was represented in their system It is difficult to draw conclusions Collapse may be a factor in regulating resistance in veins other than those of the limb but there must be many conditions when any such regulation of venous resistance by distension is impossible In congestive heart failure for instance regulation of venous resistance by partial collapse appears impossible Do you think that this is a correct assumption Dr Stead?

*Stead* Yes

*Bazett* If this is so and blood flow is reduced from failure the pressure gradient must be reduced proportionately and the gradient will not be mechanically maintained by a significant decrease in the passive distension of the vein Nor do I believe that there is likely to be any significant active constriction or dilatation in large congested veins

*Stead* I take exception to that

*Bazett* I wish to emphasize that in congestive failure any decreased flow must be accompanied by a more or less proportional reduction in the pressure gradient between the capillaries and the right auricle unless venous resistance is increased by venous constriction in spite of the congestion Such a statement need not imply a raised venous pressure relative to atmospheric pressure for capillary pressure may be low and venous pressure cannot exceed capillary pressure (except from gravity effects) If effective venous constriction is absent then with decreased cardiac output this pressure gradient must be reduced, and if capillary pressure is not subnormal venous pressure must be above normal Mathematical laws cannot be broken There are always two possibilities present there is a chance that mathematics is being misused and a second that even when mathematics is correctly used the principles involved may not be adequately explained so that the calculations become applied improperly to other conditions through lack of proper definition

I would like also to bring forward the possibility of multiple interlocking controls for any given vessels and of different reactions in apparently similar vessels to a single stimulus Pappenheimer and his group (12) have demonstrated that perfusion of an isolated limb (without reflexes) with cooled blood can cause constriction of arteriovenous anastomoses and of superficial

cutaneous arteries capillaries and veins which is associated with a dilatation of the deeper vessels including the veins There appears to be a reciprocal mechanism even in the direct reactions of the vessels

Because superficial veins can be observed to constrict to cold the assumption is made that this also happens in the case of deep veins It need not be always true In the cold venous return is along deep veins and it is possible that these are dilated Such a reaction would aid in the precooling of arterial blood in transit to the periphery which now appears an important item in the conservation of heat in cold conditions

In exposure to cold temperatures in peripheral arteries such as the radial or dorsalis pedis fall to 25° 21°C and probably lower as the result of this exchange of heat between the inflowing warm blood and the cool blood returning from the periphery in venae comites This internal exchange of heat decreases the heat lost by the arterial stream to the environment (1) As soon as the individual is exposed to heat any such precooling would be disadvantageous (2) Venous return occurs through the network of superficial veins where further cooling rather than rewarming develops in the returning blood Possibly the deep venae comites are actually constricted in such a condition The methods of control through which the alterations of the return path are accomplished remain almost unknown

Similar methods of control are likely to function during muscular exercise The blood supply to the skin passes through the muscle and must carry directly to the surface some of the heat produced Also you can notice in an athlete finishing a race that the superficial veins are fully dilated and distended but a few moments after completion of the race they become scarcely visible It is possible that muscle activity so compresses the deeper veins as to force the main return stream to follow superficial paths Then the heat from the muscles would be carried directly to the surface and any large increase in the skin circulation proper might be unnecessary Nor can any of these changes in veins develop without considerable alteration in their vascular capacity Such capacity changes must be balanced by opposite changes in other areas or else blood volume would have to alter significantly I have little doubt however that superficial return of limb blood when heat loss has to be favored is a general rule

*Shorr* What about the case of Graves disease?

*Bazett* I should think it must be present there It can certainly be seen in fever A person with a temperature of about 40°C (104°F) or more normally has the superficial veins constricted and empty As soon as the temperature begins to fall these superficial veins open up and carry a large proportion of the blood How far controls are specifically venous and how far changes depend on arteriolar reactions is uncertain The concept of venous control cannot be excluded from consideration The real data available are few but Pappanheimer s observations on excised limbs appear to be significant

*Stead* Did I understand you to say that because the veins appeared dilated in congestive failure that you did not think they would contract?

*Bazett* I would think that the veins would contract though possibly not effectively I find it hard to believe that they could dilate more Suppose that a congestive failure case had his cardiac output reduced to some 4 liters a minute Then venous pressure must be raised relative to capillary pressure although a definite absolute increase in venous pressure could be absent Venous pressure could be kept low by an active constriction of the venous path raising venous resistance and steepening the gradient This I consider improbable It could also have a low value if capillary pressure were low In the presence of protein leaks, on one side and of tissue fluid pressure raised by edema on the other it is possible for capillary pressure to be raised lowered or unchanged

*Schroeder* Cannot venodilatation be produced even beyond this limit? When subjects are centrifuged at 5 or 6G there may be tremendous swelling of veins beyond the limits of their normal capacities At operation when a renal vein is partially obstructed it will balloon up to enormous size The vena cava also will balloon with obstruction more like a rubber balloon than a structure with a definite elastic limit until the end point is reached

*Bazett* I am assuming that there occurs a rise in volume without a rise in pressure That seems to me improbable

*Stead* Are these conclusions you are drawing based on the fact that you must keep the circulation moving or are they based on actual observations on veins?

*Bazett* The data are best represented by the electronic formulae interrelating capacity impedance etc On a simpler plane more within my reach you have pressures which resemble voltages One has to assume that capillary pressures must approach a more or less constant average value if a steady state is to be maintained If there are resistances on each side the resistances must both be changed in a similar manner unless the capillary can be allowed to change enormously Laws similar to Ohm s law have to be obeyed Sometime ago I devised a schema for teaching to the students quantitative regulation of the circulation I tested my instructions and found that they showed a complete absence of any knowledge of the fundamentals of the circulation I had to correct my errors These all were dependent on the need for matched arteriolar and venous resistances If the capillary pressure is to be kept constant you have to balance shifts in resistances

*Shorr* Is it possible Dr Bazett that a change could occur in the number of open capillaries?

*Bazett* That is possible It all depends how one defines venous or postcapillary resistance I am calling resistance postcapillary where it is distal to an imaginary point where there is an osmotic balance I don t necessarily specify where that is because I am not sure in one condition it well may be nearer the arteriolar end of the capillary and in another nearer the venule

*Shorr* I bring this point up because of observations that Dr Zweifach and I made on mesentery of rats with hypertension in which there was a pronounced hyperplasia of the capillary bed Apparently there can be an adjustment in this condition

*Bazett* I am not certain as to what the anatomical arrangement is As long as I define capillary as the point of balance the statements have at least a limited truth but the word capillary may not be used in its correct sense

*Katz* Could you and Dr Stead agree on this point? It has been reported that the central venou pressure rises more than the peripheral venous pressure in congestive failure I am assuming two things (1) that the capillary pressure does not change in this condition and (2) that the veins between the capillaries and the right auricle are distended With the same rate of flow there must therefore be less of a pressure drop between the

*Shorr* What about the case of Graves disease?

*Bazett* I should think it must be present there It can certainly be seen in fever A person with a temperature of about 40°C (104°F) or more normally has the superficial veins constricted and empty As soon as the temperature begins to fall these superficial veins open up and carry a large proportion of the blood How far controls are specifically venous and how far changes depend on arteriolar reactions is uncertain The concept of venous control cannot be excluded from consideration The real data available are few but Pappanheimer s observations on excised limbs appear to be significant

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*Bazett* I am assuming that there occurs a rise in volume without a rise in pressure That seems to me improbable

*Stead* Are these conclusions you are drawing based on the fact that you must keep the circulation moving or are they based on actual observations on veins?

*Cournand* Ferris and his group have done considerable work on this subject He has studied the correlation between volume changes and pressure changes in peripheral veins This was published shortly after the war in the J C I the senior author being Pyder I believe

*Stead* It has been shown by Dr Blumgart and his group that the venous pressure in the foot falls when you raise the foot slightly but on further raising it the pressure rises In these collapsed veins, you are measuring some aspect of tissue pressure rather than venous pressure

*Bradley* When you place such a cuff around the arm and halt the arterial inflow both the venous and arterial pressures will come down Then if you squeeze your hand the venous pressure will rise above that of the arterial pressure I wonder about the effect of valves in this whole system?

*Bazett* Anatomists tell me that there are no venous valves except in the limbs but I am still skeptical I wonder whether that is true It is difficult to believe that there is no muscular pump in the lumbar vessels

*Katz* Does it really matter whether there are valves everywhere? A few valves in strategic situations as for example at the inlets and outlets to the ventricles are adequate to maintain unidirectional flow

*Bazett* I agree with you a few valves would do it There is not enough blood to have the whole vascular system on a completely filled basis and one must assume that for the majority of the time most of the veins of the normal individual are semi collapsed A considerable increase in blood volume would develop if these were filled

*Lamport* There is another aspect that should be considered in respect to valves

When pressure is suddenly placed on a branching system like the venous system with tributaries entering larger and larger vessels blood will always spurt towards the larger side because of the greater resistance the branching and other phenomena on the small vessel side In the kidney the same phenomenon may aid

in propelling urine in the collecting tubules (10) * With the introduction of a sudden pressure pulse externally it seems to me that you will still have something like a pump even without valves Step on the garden hose connected to a sprinkler after it has just been disconnected from the faucet Water will gush out of the open end and little will come out of the sprinkler That is analogous to what is happening in our extremities

*Katz* Momentum and inertia also play significant roles Wiggers and Feil have shown that even with mitral insufficiency unidirectional flow still occurs

*Fremont Smith* It is not just a question of being pressed on but every time for instance that the arm is straightened out the veins on the flexor side are stretched and those on the extensor side contract and when the elbow is flexed the reverse takes place The volume of an elastic tube increases on elongation Therefore every time the veins are stretched they increase in volume and act as a reservoir and when they contract they decrease in volume pumping the blood towards the heart

*Bazett* I think that is sound The valves would come in as an accessory mechanism not as a primary mechanism

*Fremont Smith* I would just like to note at this point that this thing is strictly true in the inferior vena cava which is elongated to a very considerable degree each time the diaphragm rises and shortens and thickens when the diaphragm goes down in inspiration Thus the inferior vena cava acts as an accessory pump as a reservoir for blood at the time when blood does not flow readily into the chest i e in expiration while in inspiration the vena cava shortens and helps to drive blood into the chest when the pressure in the chest is negative The superior vena cava lying within the thorax acts in a reciprocal manner because it becomes a reservoir for blood during the time the diaphragm goes down but contracts and discharges blood into the right heart when the diaphragm goes up We thus have a double acting pump from the elongation and shortening of the superior and inferior venae cavae

*Katz* A similar and important effect occurs in the pulmonary tree About 25 years ago I was interested in this subject and

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* The references in Dr Lamport s discussion of this and subsequent papers will be found on page 131

showed that during inspiration the capacity of the pulmonary tree increases during expiration it decreases The lungs in this sense act as an auxiliary pump for the circulating blood [Katz L N and Gauchat H W *Arch Int Med* 33 *371 (1924)*]

*Fremont Smith* I would like to carry this analysis one step further The same type of change will occur around the alveolus where the network of capillaries will also be elongated with each inspiration and shortened with expiration During rest expiration is followed by an appreciable pause which is longer than the pause at the end of inspiration During exercise this is reversed there is no pause at the end of expiration and a slight pause I believe at the end of inspiration The result is that not only are the alveoli capillaries and pulmonary vessels in general elongated to a much greater degree in the deep respiration of exercise but they are elongated for a considerably larger fraction of the respiratory cycle Thus these vessels especially the veins act as an accessory pump and diffusion through the alveoli capillaries during the in spiratory phase should be more rapid since these vessels are elon gated stretched and hence must have thinner walls This may explain a dilemma pointed out by L J Henderson many years ago that oxygen intake and carbon dioxide output in the lungs in exercise appear to be greater than could be accounted for by the known factors The thinner walls of the alveoli capillaries during the deeper and longer inspiratory phase in exercise might provide an additional factor to explain this discrepancy

*Lamport* Dr Bazett mentioned the double set of veins lying along the arteries Their proximity may be more important in terms of the pulsation of the artery being transmitted to the venous blood than the matter of temperature transfer because the pulsing artery would tend to milk venous blood centrally I think the partition of flow produced by a pulse might be as much as two to one perhaps twice as much venous blood would flow centrally as peripherally

*Bazett* The Germans have emphasized that point There is a side issue which may be of interest Dr Edholm is interested in the giraffe and once dissected one At autopsy the veins in the leg were found to withstand pressures up to 200 300 mm The internal jugular was full of valves all the way down It is an in

teresting fact that valves do exist simply for such relatively rare situations

I think you will all agree that we know surprisingly little about the physiology of veins

*Cournand* I would like to call attention to something which is rather interesting in regard to the venous pressure, namely a difference in pressure existing between the brachial vein and the right auricle The pressure in the brachial vein under normal conditions is higher than in the right auricle (drawing on the board) If you change the pressure in the heart by cough the pressure rise will not be reflected in the peripheral vein I am speaking only of the peripheral veins beyond the subclavian and not of the large intrathoracic vessels When you deal with a patient who is in cardiac failure with a distended venous system the pressure gradient between the peripheral vein and the right auricle disappears completely As a matter of fact if the mean pressure is taken at both points it appears that the pressure in the peripheral vein is lower than that in the right auricle However, if you take simultaneous tracings registering the cyclic changes in the right auricle they show clearly that the flow must be an intermittent one A pressure gradient from the peripheral vein towards the heart exists only at the beginning of systole and at the beginning of diastole These remarks are intended to emphasize the importance of cardiac dynamics on the peripheral vein flow under certain conditions

*Lamport* Dr Bazett and I have discussed the use of a term other than resistance in hemodynamics and we both agreed that there was a concept much more useful than resistance but the difficulty was that historically resistance was so well entrenched in the physiological literature and elsewhere that there was almost no hope of replacing it It is probably optimistic on my part to hope that I can convince other people to try to use some other term but I think conductance which is just the reciprocal of resistance —you divide 1 by resistance and you get conductance—has great advantage in physiology and in clinical medicine I shall try to explain why

Resistance you recall is defined as pressure divided by flow (meaning volume flow rate) Just as in electricity conductance

is defined as the reciprocal of resistance If we say conductance equals 1/resistance we have conductance equal to flow divided by pressure and if we call flow I and pressure P so that we can handle them easier we have I/P for the conductance C Suppose we are considering several organs at once as we so often do in the body and we want to study their separate hemodynamic characteristics Let us take the first organ and call $C_1$ its conductance Then $C_1$ for the first organ is equal to the flow through that organ $I_1$ divided by P the pressure and the flow through the second organ is C which is equal to I also divided by P and $C_3$ is equal to $I_3$ divided by P Suppose you enumerated the conductances of all the organs in the body If you add them up you have

$$C_1 + C + C_3 + \quad + C = (I_1 + I + I + \quad + I)/P$$

But $I_1 + I + I_3 + \quad + I$ is the total blood flow in the body (we call it $I_b$) through all the organs so that

$$C_1 + C + C_3 + \quad + C = I_b/P = C_b$$

the conductance of the body Thus *the conductance through any group of organs is the sum of their conductances* because they all are perfused at approximately the same pressure so that there is a common denominator when summing the expressions for conductance through any group of organs

In the chart Dr Bazett presented he had large and small resistances but the total resistance was the *smallest* of all

That is because parallel resistances like those of the organs of the body can be replaced by a single equivalent resistance only after first computing their reciprocals just as you do in electricity If we have parallel resistances in electricity we must get the sum of their reciprocals and invert it The same problem arises in optics We know that to replace two lenses with a single one of the same focal length we do not add their focal lengths but add instead the reciprocals of their focal lengths 1 over $F_1$ plus 1 over F equals 1 over F Opticians call the reciprocal of the focal length diopters corresponding to our conductance and use it in preference to focal length because of its convenience

*Fremont Smith* Don t you have $P_1$ P and so on?

*Lamport* We are dealing with crude measurements and are justified in considering blood pressure the same for all organs

*Fremont Smith* The cells might get mixed up again in the venous side

*Lamport* Branching in the circulation is important I think one function of branching is to stir up and mix the blood and prevent too much axial streaming

*Fremont Smith* May I ask another question in this connection? As an arteriole shuts down and narrows its radius does the fact that there are red cells present and axial streaming tend to increase the Poiseuille s effect or decrease it? Is the increase in resistance from constriction more than it would be under Poiseuille s law or less?

*Lamport* As an arteriole shuts down the effect of deviation from Poiseuille s law is to make less blood flow for a given pressure than would otherwise be the case always assuming normal hematocrit And yet to begin with under normal conditions *more* blood flows through arterioles under a given pressure than would be the case if blood followed Poiseuille s law as it does in large bore tubes It seems as others have already noted (19) * that blood becomes increasingly fluid as the bore of the tube decreases reaches some maximum fluidity and then becomes less fluid as bore is further decreased Arterioles operate in the latter region with blood of normal hematocrit

*Ogden* When you pointed out that the branching in the arterial tree tends to promote stirring is there evidence that ordinarily there is turbulence at any of the branches?

*Lamport* I do not think there is good evidence of turbulence and the calculations all show that the Reynold s number which is supposed to characterize the tendency towards turbulence is below the required range I must say that Coulter and Pappenheimer feel that turbulence may be present at some portion of the vessel cross section perhaps only at the vessel wall (4) * Frankly I am not convinced by their argument but it should be borne in mind that this possibility has not been disposed of

*Fremont Smith* May I go one step further According to Poiseuille s law the flow varies inversely as the fourth power of the radius Blood is a fluid which changes its viscosity in its pas

*See Page 131

sage through the vascular tree If you knew its viscosity would you not be able to apply this law to its known new viscosity?

*Lamport* I should have said that the word 'apparent vis cosity has been used to obtain a new coefficient to adjust the failing Poiseuille s law Apparent viscosity is computed on the basis of applying Poiseuille s law and it becomes simply a correction factor That correction factor varies with the dilation of the vessel so that would mean that you do not have an invariant correction factor It would fluctuate and not characterize the fluid alone It would be dependent on the fluid on the vessel size and on the rate of flow a most embarrassing array of variables for a constant to depend on

What has been shown is this The flow I is proportional to the pressure drop P in a properly isolated mammalian limb when perfused with Ringer solution or plasma but if you substitute blood this is no longer correct and you get this I the flow is proportional to P to the nth power (7) *

$$I \propto P^n$$

You need a completely new law I have done some work with it Pappenheimer and his colleagues are working with it There are different ways of handling the problem I have tried to develop the proportionality constant in terms of the radius of the vessel It turns out that—this is going afield—it is possible to make a tentative approximation for this constant (11) * Further confir mation is required

*Fremont Smith* If a given arteriole halves its diameter will that have a greater or lesser effect on the flow than you would have expected had it obeyed Poiseuille s law?

*Bazett* Less effect unless you get to where the capillary produces a new effect This depends on the diameter of the tube being smaller than that of the corpuscle The corpuscle has to undergo distortion

*Lamport* If pressure is held constant the effect of halving the radius of the arteriole is to reduce blood flow through it pro portionately *more* than would be the case if blood were a New tonian fluid obeying Poiseuille s law This excessive effect due to

See Page 131

the pseudoplasticity of blood is greater the *lower* the perfusing pressure

For small changes of vessel caliber and a fixed region of tissue and sample of blood a logarithmic formula has been developed which may cast some light on this question (11) *

$$I \propto \frac{R^3 + n}{n + 3} P^n \mu^n$$

If the changes in R are small so that concomitant changes in n can be neglected with P held constant we have

$$I \propto R^3 + n$$

Poiseuille s law corresponds to the special case in which n = 1 For blood since n is greater than one we see that under the conditions outlined the formula agrees with the statment that changes in blood flow with change in vessel caliber exceed those predicted from Poiseuille s law ?

*Fremont Smith* Thus with vasoconstriction the effect on blood flow is greater than that which would be expected on the basis of Poiseuille s law ?

*Lamport* Yes The peculiar fact is that the viscosity of blood relative to water in large vessels and in glass tubes is between 4 and 5 but that in perfusion of the animal limb its overall value is about 2 2 It is a tribute to the design of the blood vascular system that blood in the big vessels is viscous enough to prevent turbulence with its resulting inefficiency while in the smaller vessels it becomes twice as fluid permitting smoother flow control and distribution

*Ogden* What is the limiting value of n in the logarithmic equation you wrote on the board?

*Lamport* One is of course the lowest value corresponding to plasma The highest reported by Green and his co workers was five (7) *

*Katz* Jochim has shown that the resistance can vary from the first to the fifth power So I thought the limiting factors for n would be 1 to 5

*Lamport* Using Green s range for n of 1 to 5 with 2 being most usual we see from the formula that flow with fixed pressure would vary as R

*See page 131

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*Goldblatt* Now Dr Katz will discuss the hypertensive syndrome

# HEMODYNAMICS OF THE CIRCULATION IN HYPERTENSION

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My task is to integrate isolated facts which all of you are familiar with about the dynamics of the circulation in high blood pressure I shall deal with clinical essential hypertension with experimental Goldblatt hypertension and with canine spontaneous hypertension I would like to emphasize at this time that considerable work remains to be done in spontaneous hypertension It should not be confused with so called experimental neurogenic hypertension

I shall deal with complications such as heart failure renal failure or arteriosclerosis only incidentally as they clarify or complicate the picture Several studies in the past have not excluded these factors and hence have led to apparently contradictory results There is not sufficient time to deal with shortcomings and errors in methods of measurement I need only mention that frequently data are uninformative or misleading simply because of the inherent inadequacy of the methods employed

As far as I know the cardiac rate and output per minute is unchanged in hypertension (7 15) The blood viscosity is not significantly altered in hypertension (4 6) The venous pressure and capillary pressure are apparently not increased (2 4) The circulating blood volume and the total blood volume are unchanged (1 15)

*Stead* You include the arterial blood volume?

*Katz* The systemic arterial blood volume I calculated as being 250 cc I noticed that Dr Bazett s figure for this is 400 The change when the blood pressure is elevated, is not significant This system has volume elasticity Of course you are familiar with the pressure volume (P/V) relationship Recently we did some work on this in dogs (8) We used diodrast to obtain *in vivo* and *in vitro* data on the acute changes in the P/V ratio for the descending thoracic aorta The accompanying Figure 9 is a composite of the data obtained on 7 intact animals Acute increase in

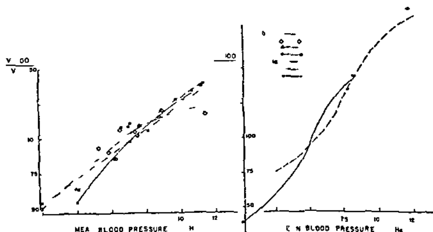


FIGURE 9 P/V curves as calculated for the descending thoracic aorta in seven living dogs

mean blood pressure of 100% or more yields a 25 75% increase in the aortic volume Thus it is obvious that *acute* elevations of blood pressure may increase the arterial blood volume However the magnitude of the changes is such as to be insignificant in relation to the *total* circulating blood volume It depends entirely on whether you consider the change in relation to arterial blood volume or to total circulating blood volume Thus if the total circulating blood volume is five liters and the arterial blood volume is a quarter of a liter and the latter doubles this would be a 100% increase in arterial blood volume but only a 5% increase in total blood volume

Moreover our data are by no means a complete portrayal of the changes in aortic volume in acute hypertension Thus Wiggers and Wegria in studies using the aortagraph recorded a more complex response at the root of the aorta (20) During acute hypertension due to nervous and hormonal agents the aorta first expands and then diminishes in size These changes in the intact animal are probably the result of elastic or muscle elements in the vessel wall which respond actively to the complex stimuli evoked Finally it is questionable whether any increases in arterial blood volume occur when there is *chronic* elevation of blood pressure It is not valid to assume the same P/V relationships in chronic as in acute hypertension

Hence in terms of total blood volume even this large increase in arterial blood volume would not be very important Although percentage wise the increase in arterial blood volume is great the actual number of cc of blood involved is too small to be important

*Stead* I would like to take exception The arterial system is a region where an indisputable change occurs Its relative importance cannot be dismissed It could be looked at in several ways An increase in the arterial blood volume could conceivably be the mechanism by which the whole syndrome started

*Katz* That is one possible way However you are taking a continuous process and stopping it where you wish What is cause and what is effect? What produces the increased arterial blood volume if it is not secondary to increased resistance in the arterioles? It has been my understanding that the arteries offer little resistance to the flow of blood from the heart to the arterioles even in hypertension Prinzmetal and Oppenheimer showed that the fall in pressure in the large and small arteries was the same in hypertensive and normal subjects (13) They concluded that there was no increased resistance of the arteries and that hypertension must therefore be due to an elevated resistance in vessels smaller than the digital artery In general the consensus has been that *mean arterial pressure is not affected significantly by changes* in the large arteries I know of no facts refuting this view

*Bazett* Another point to be taken into consideration is that in dealing with older people you have about twice as much blood in the aorta as you have in younger people

*Katz* In other words you are supporting my statement that factors such as arteriosclerosis may make the amount of blood in the arterial vessels much higher The P/V alterations occurring under these circumstances are quite distinct from those seen in uncomplicated essential hypertension In brief loss of arterial *elasticity due to arteriosclerosis leads to* a pattern of *increased* systolic pressure with increased pulse pressure unchanged or reduced diastolic pressure and little change in mean pressure Although the arterial blood volume is increased diastolic hypertension does not occur In man this pattern is often superimposed as a secondary complication of essential hypertension producing an increase in pulse pressure Such complications are not seen in nephrogenic or spontaneous hypertensive dogs since they remain

free of arteriosclerosis I know of no data on arterial blood volume in such chronic hypertensive dogs There seems to be little basis for relating chronic hypertension to changes in arterial caliber

In this regard it is worth referring to coarctation of the aorta Today it is questionable whether the hypertension recorded in many patients with coarctation is the result of mechanical obstruction with shunting of increased volumes of blood to the upper extremities Experimental and clinical evidence suggests that a Goldblatt mechanism may be involved

If the cardiac output and the total blood volume are essentially unchanged in hypertension then it follows that the total peripheral resistance is increased The increase in peripheral resistance is not due to altered viscosity It is true that in the presence of polycythemia and under other circumstances (e g where Knisely would have us believe there is sludging) there would be a change in viscosity These special circumstances do not prevail in most cases of hypertension There is no reason to believe that turbulence is a factor in the altered peripheral resistance As already indicated the increase in peripheral resistance is not arterial Its primary site is arteriolar

Having established these basic facts about the increased peripheral resistance we must ask How come? Before going into this it is worth while pointing out several characteristics of the peripheral circulation The peripheral circulation is essentially a group of circuits in parallel Not only are the circulatory pathways of different organs in parallel but even within a single organ or tissue the circulatory pathways are also in parallel This immediately suggests the possible absence of homogeneity The significance of this possibility has been emphasized for the hypertensive kidney Thus when we measure organ flow we are not necessarily measuring the flow through any given part of the structure We obtain the mean flow and when we state that the flow is unchanged we do not necessarily mean it is unchanged in all parts of an organ In some parts of the structure the flow may be increased to the same extent that it is decreased in others Hence I would like to emphasize the concept of parallel circuits within organs

Further a change in resistance in one organ may *per se* cause a redistribution of blood In other words if vascular resistance is

increased in one organ and circulatory continuity of flow is maintained, it is obvious that some blood must be diverted into other organs if the left ventricular output remains unchanged Going into other organs it must of necessity alter the P/V ratio for their vascular bed Vascular distention will result in an increased blood vessel radius Since the vascular resistance varies inversely as the radius anywhere between the first and fifth power, the vascular resistance in those organs being distended will decrease without any other intervention In this way purely mechanical factors *per se* may bring about changes in flow

In other words I am trying to stress the idea of flows in parallel through one organ or another This concept can apply to the Zweifach schema of the peripheral vascular bed to the single organ and to the whole body

*Bazett* The real resistance is in the arterioles Then the increase in pressure is only effective in stretching it inversely as the radius because the tension on the wall varies as the pressure multiplied by the radius The smaller the vessels are the more difficult it is to stretch them significantly and to lower the resistance by a rise in pressure

*Katz* This may be so theoretically I have been able to perfuse the coronary circulation in isolated heart preparations with a second set of resistances in parallel using the old Starling method By mechanically increasing the extra coronary resistance and thereby decreasing the blood flowing through it the flow through the coronary circuit is seen to increase although the total head of pressure in the aorta and the total ventricular output both remain unchanged the former within 1 mm Hg Therefore the facts are that in a denervated preparation the purely mechanical effect is sufficient to dilate the coronary circuit when the extra coronary circuit in parallel is narrowed

*Bazett* Are you sure it is not due to metabolites?

*Katz* I am not at all certain You have found a flaw in the argument

*Fremont Smith* In situations where innervation is operating certainly what Dr Bazett said is more likely to apply than not Dilatation of the arteriole is not a function of pressure in the arteries but a function of vasomotion active dilatation and constriction mediated by nerve or chemicals at the arterial level

*Katz* I would agree that under those circumstances this may be true

*Kety* Since we are discussing mechanical factors I agree with Dr Bazett that I am not terribly impressed with the ability of the rise in pressure as a result of occluding a parallel circuit to dilate the other members of the circuit I should think by increasing the velocity of flow through the remaining circuits one would produce a greater effect upon the resistance which is left than one would by altering the diameter of those vessels

*Schroeder* I think you are neglecting something that was discussed this morning A partially occluded local resistance is not represented by just a clamp on a tube It must be represented by 2 clamps one for the constriction and one for the arteriolar bed What happens in the segment between the 2 clamps depends upon the rate of the inflow into the segment and the rate of outflow out of the segment If its obstruction is increased you may get a good flow at a smaller pressure if the arterioles are dilated On the other hand to maintain pressure in the segment the arterioles must be constricted and flow is therefore reduced In such a system you can maintain pressure at the expense of flow or maintain flow at the expense of pressure but you cannot have both

*Katz* I can agree to all this but I consider it beside the point

*Fremont Smith* It may not be important with respect to your theme but might be with respect to particular problems arising from it

*Katz* That is a fair statement To carry through the theme that when the flow decreases in one organ it will increase in others is primarily what I am interested in for the moment

*Fremont Smith* May I paraphrase what you are saying? In a mechanical fluid dynamic system if flow decreases in one part and no other changes occur an increase must occur in the other You are not implying that the increase in the other has to be a passive one It can well be an active one It may produce an even greater increase in flow in the one than the original decrease in the other

When nor adrenaline is administered to an individual vasoconstriction develops in some vessels and in spite of the vasoconstriction and increased heart rate there is a fall in diastolic blood

pressure Obviously a redistribution of blood must have taken place with a greater dilatation of the bed which opened up than there was constriction in the bed that is constricted Although there is an increased resistance in one bed the decrease in resistance in the other bed is greater This would be the only possible way to account for the fall in diastolic pressure The same type of change occurs in typhoid bacterial fever where there is complete shutdown in much of the skin increased heart rate and yet a fall in diastolic and systolic

*Katz* I agree that the factors involved in any particular circumstance are extremely complex I intended only to make a simple point viz when flow in one organ is decreased and the output of the pump is the same the flow through other organs must of necessity increase

The next point I would like to make is that flow is laminar This is brought up in order to bring attention to the fact that one lamina of blood or one tube of blood flows faster than the other Hence shears develop frictional resistances Therefore not all the frictional resistance in vessels is between the blood and the vessel wall but some is between the various layers or tubes When one considers resistance this should be taken into account

Dr Bazett has shown that a uniformly distributed 12% decrease in the circumference of a blood vessel would increase the resistance by about 50 percent The point I wish to make is a qualitative one i e that those who look at the microscopic appearance of blood vessels and say I cannot see any change in cross sectional area may readily miss significant changes In other words small changes in circumference universally distributed may produce striking changes in resistance

I would like to emphasize that the resistance of a blood vessel varies from the first to the fifth power of its radius If the radius were doubled then the resistance could be halved or it could actually go down to as little as 1/32 of its previous value Again I am trying to point out the considerable effect of relatively small changes in vessel caliber on the peripheral resistance

If we may assume that the state of skin capillaries is a good example of what prevails generally in the capillaries in human hypertension it would appear that they are not altered

*Zweifach* I do not believe that it is possible to generalize from observations made on the vessels in the skin to vessels in other organs of the body Observations carried out on the skin and splanchnic tissues simultaneously in a variety of experimental conditions have indicated considerable differences both in the degree and in the direction of the vascular changes which develop in these two sets of vessels

*Shorr* We have seen striking changes in the capillary bed of the mesentery of the rat during the development of hypertension

*Page* Otfried Muller has described vascular changes in the eye in a monograph on this subject

*Katz* Are the changes in the conjunctiva which have been described a form of arteriosclerosis?

*Goldblatt* I am not prepared to state that they are arterio sclerotic That would depend upon the definition of arterioscle rosis I think it would be better for the present at least to say that there are recognizable pathological changes in the vessels

*Zweifach* Why must the presence of vascular dysfunction or abnormalities be measured only by visible pathological changes? Why cannot functional alterations exist in such vessels? Dr Katz states that no visible alterations are seen in the capillary vessels of the skin and implies that the capillary bed is therefore per fectly normal This does not rule out the presence of meta bolic changes which are after all the forerunners of pathological changes The latter are visible endpoints of a series of biochemical disturbances whose presence cannot be detected by ordinary histo logical procedures

*Goldblatt* Pathological changes can be seen

*Zweifach* I would like to make my point clear I do not dis pute the evidence for or against definitive pathological changes in the peripheral vascular bed I would like to lay stress on the con sideration that the absence of such changes does not necessarily indicate a normal vascular bed from a functional point of view In measuring the diseased or abnormal state other yardsticks should be employed In rats and dogs functional alterations ap pear early in the peripheral vascular system during the develop ment of hypertension long before any visible structural changes have developed

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vascular readjustment must have occurred to make this possible The pressure in the arterial tree is elevated the arterioles are narrowed and despite this the circulation through the capillary bed appears normal The pressure relationships influencing fluid exchange between the capillaries and the tissues are being maintained at normal levels since no obvious manifestations of edema are present All of this could only be possible through the active participation of the peripheral vascular bed in readjusting the circulation distal to the arterioles in the hypertensive state We are still however in the dark as to whether the changes in blood pressure preceded any changes in the peripheral vascular bed or whether functional disturbances in the peripheral vascular bed necessitated a change in the feeding arterioles in order to stabilize the circulation and maintain homeostasis

*Katz* We may pause to re state another question Do the central arteries contribute to the resistance? You will find that my former chief Wiggers stated on the basis of increased pulse pressure that the changes in hypertension are in part attributable to decreased elasticity of the arterial walls (18) We have already discussed the character of the pulse under such circumstances The changes are not those of essential hypertension *per se* Wiggers himself concluded that increased resistance offered by the arterioles was the fundamental process in hypertension if not the only one There is almost no evidence that conclusively proves the existence of primary changes in the musculo elastic tissue of the large arteries To repeat there is no denying the secondary role of arteriosclerotic complications With arteriosclerosis as Bazett pointed out the pulse pressure increases with a similar pulse volume and mean pressure This change in the pulse wave contour contributes to increased pulse pressure in clinical hypertension One might even accept the concept as Bradley has noted that increased arteriolar resistance with elevated mean diastolic pressure leads to continuous distention of the arteries This reduced distensibility like arteriosclerosis may contribute to the increased pulse pressure of hypertension

Peturning to the main theme I would like to leave you with two concepts concerning the control of the peripheral circulation The first relates to the control exercised by virtue of the buffer nerves This mechanism responds to acute rises in blood pressure The evidence to date indicates that in the three forms of hyper

tension which we are considering there is no decrease in the ability of the moderator nerve mechanism to compensate for acute elevations of blood pressure (2, 4) It apparently functions normally but set at a higher level Of necessity, therefore we must assume that a derangement somewhere else along the circulatory system accounts for the hypertension

The second factor exercising control over the peripheral resistance is that by virtue of metabolic factors Whenever potential ischemia or hypoxia arises in an organ the metabolic alterations tend automatically to react upon the local blood vessels altering the P/V relationship so that blood flow tends to remain commensurate with need Therefore in hypertension it is not surprising that as a first approximation the blood flow to every organ is within normal limits The broad principle is that in the presence of increased resistance flow is within the normal range in hypertension because of this local metabolic adjusting mechanism keeping the flow of blood within the limits of need

Having gone this far I must say that the only sign of hemodynamic change in the animal with hypertension is a change in contour of the central pulse or peripheral pulse This is the kind of curve which Wiggers has called the high resistance curve Whether you call them reflected waves or standing waves they are due to narrowing of small vessels in the periphery

The left ventricle is hypertrophied but its output is unchanged Its hypertrophy is due at least in part to increased resistance load The heart has three kinds of loads a resistance load which is the resistance against which it empties input load like input of an electronic circuit, the amount of blood returning to it and various hidden loads such as those which occur in valvular disease Hypertrophy in uncomplicated human and canine hypertension compensates for the increased resistance load sufficiently so that dilatation and tachycardia the other two compensatory mechanisms do not come into play This is well known in the hypertensive dog or man Dilatation and tachycardia occur only with coronary sclerosis which in my opinion is a complication of high blood pressure wherein the reserve of the heart is encroached upon too much and the heart begins to show the evidences of heart failure usually of the congestive variety

*Cournand* May I raise a question with regard to the hypertrophy of the heart in hypertension? Do you think that the volume

of the cavity might change with hypertrophy and that in turn may have some effect upon the filling pressure that which you call the input load?

*Katz* The possibility exists I personally don t believe it The few studies with diodrast that we have done have not convinced me that the configuration of the cavity is altered in hypertension with hypertrophy

*Cournand* I was just trying to introduce some recent information Some work has been done on this subject by Lowe from Australia who spent some time in this country recently

*Katz* If I understand your question namely what would be the P/V relationship in the fully relaxed hypertrophied left ventricle I would agree with you it must of necessity be changed assuming that the wall thickens As a matter of fact we demonstrated such changes in P/V relationships in acute hypertension produced by compressing the aorta (19) However if you mean that the cavity is increased in chronic hypertension with hypertrophy I frankly am not convinced that this would play a role It seems to me that from the X ray picture there is no reason to believe that the heart is enlarged If the wall is thickened and the outside diameter is not enlarged the volume of the cavity should be less rather than more In secondary dilatation I would agree with you

That leads me to one thought which I had meant to bring out I am delighted Dr Cournand that you have mentioned hypertrophy I do not know and I am not certain that anyone knows what causes hypertrophy My own impression is there are three things associated with it relative ischemia or hypoxia relative dilatation and relative increased work I do not know which factor is most responsible One of the important problems remaining in the field of circulation is the mechanism causing hypertrophy of the heart

*Schroeder* Hypoxia is not necessarily the cause of cardiac hypertrophy One would expect hypoxia with coronary sclerosis but the usual result is not hypertrophy although there are exceptions

*Goldblatt* Dr Schroeder s statement is not substantiated by clinical experience

*Katz* I agree with you

*Goldblatt* It is my own belief that the true cor bovinum the really large heart, occurs in individuals who have not only high blood pressure but also coronary sclerosis I have also personally observed unquestionable cases of hypertrophy of the heart un associated with hypertension but with definite coronary arterio sclerosis of the obliterative type

*Katz* I am in wholehearted agreement with Dr Goldblatt We have produced extensive coronary sclerosis in normotensive rabbits We had no reason to believe that arteriosclerosis of the central vessels would affect the heart Yet we found hypertrophy (10) Furthermore Palmer working with Parkinson and Sokolow in San Francisco followed normotensive patients with coronary disease and found the hearts to be enlarged One piece of work coming out of the Cook County Hospital has shown that normo tensive patients with no evidence of nephrosclerosis had left ven tricles enlarged in proportion to the degree of coronary ischemia as evidenced by coronary sclerosis There is therefore little ques tion that hypoxia or at least coronary sclerosis can be a trigger mechanism for cardiac hypertrophy

*Grollman* I believe that hypertension *per se* has a specific effect on the myocardial muscle At least our recent work has supported this view and forced us to discard the generally ac cepted mechanical notion which Dr Katz accepts In the nephrec tomized dog to be specific you get changes in the heart that certainly can not be attributed to any mechanical factors In the past such consideration of changes in the heart in hypertension has been overlooked We have demonstrated the occurrence of changes in myocardial fibers comparable to those occurring else where in the vascular system

*Katz* The possibility is acceptable but unnecessary

*Goldblatt* Are you talking about changes in weight as in dicators?

*Grollman* No Microscopic changes occurring in the myo cardium

*Goldblatt* Are you certain that you are referring to hyper trophy as we understand it or are you discussing intercellular edema or other changes which should not be confused with true hypertrophy

*Grollman* These early changes which regardless of their nature may ultimately be responsible for the observed hypertrophy

*Schroeder* In unusual situations we have seen patients with long standing hypertension who have a normal sized heart I have known of at least one case with a normal heart and with known hypertension for 20 years

*Katz* I have heard about other isolated experiences but they may represent chance variations whatever that may mean I don't think you can use that against the overwhelming evidence

I would like to continue with several other points Recent cooperative work in Bing s laboratory in Philadelphia and in the Army Chemical Center at Edgewood Arsenal Md has shown that the oxygen in the coronary sinus is very low It is through the coronary flow that the needs of the hypertrophied heart must be supplied To the best of my knowledge the oxygen uptake in hypertension is not changed in terms of the amount per 100 grams Since the mass is greater quite obviously the coronary flow in the left ventricle must be greater and therefore the coronary flow must be greater for the whole heart

*Dexter* But the mechanical efficiency of the heart is greatly reduced

*Katz* I am glad you brought up that point It would agree with Gollwitzer Meier (5) and with our own work (12) Using the heart lung preparation we found that increasing work by increasing output led to increase in efficiency while increasing work by increasing resistance tended to decrease efficiency We felt therefore that the Starling Visscher law did not always hold That discussion enters into another controversial area

To return to our theme with a decreased efficiency the coronary flow should be increased even more than otherwise Now if the coronary flow increases it must be at the expense of other systemic flows

While the work of the heart in hypertension is increased the cardiac output is not Hence the kinetic work of the heart is not changed (unless the aortic or pulmonary ring is dilated) The pulmonary flow is unchanged It cannot be changed since the cardiac output is unchanged So far as we know the blood reservoir

function of the lung is also unchanged The pulmonary pulse pressure is unchanged in hypertension and the pressure in the right heart is not changed unless failure develops Therefore if these facts about the right side of the heart are true it follows that systemic hypertension essential Goldblatt or spontaneous is unassociated with changes in pulmonary resistance I know this to be so from some experiments we did with a London cannula where we took simultaneous pressures in the pulmonary and femoral arteries in Goldblatt hypertensive dogs (11) With the advent of catheterization these results have been substantiated Recently we verified these facts in the spontaneous hypertensive dog (15)

In man the brain flow is unchanged Nevertheless the eye grounds show narrowing and some vasomotion and this would suggest that in essential hypertension there may be some sort of periodic changes in resistance not only in the eye grounds but in the brain and elsewhere

The work of Bradley and some others shows that the hepato portal circulation and hence the splanchnic blood flow is unchanged To the best of our knowledge there is no change in the portal venous pressure In the hepatoportal system there are a multitude of sphincters not only those to which Dr Zweifach was referring but many others These occur in the hepatic and splenic arteries in the mesenteric arteries and on the venous side They appear in the portal venous system where it enters the hepatic lobules and in some species at least they occur in the hepatic venous system proper

Even though the pressure in the arteries leading into the liver spleen and the enteron is elevated the pressure is still unchanged in the portal vein in the hepatic vein and in the inferior vena cava It therefore follows that somewhere before the hepatoportal bed the elevated head of pressure is dissipated

*Perera* That also applies to every area where the pressure is increased and beyond which the blood flow is normal

*Ogden* The portal pressure is unchanged? On what is that statement based?

*Katz* In acute arterial hypertension due to pressor drugs the portal pressure does not necessarily change although this depends

upon the relative changes in the two resistances that affect the portal vein pressure the primary resistance of the gut which brings the pressure from systemic arterial levels to about 20 mm Hg and the secondary resistance within the liver which reduces the pressure to that obtaining in the inferior vena cava (9) However it is probably unjustified to say anything about the portal venous pressure in chronic hypertension I am not certain that it has ever been measured

*Schroeder* Will you modify your statement to say that these statements are so in hypertension when the patient is *at rest?*

*Katz* Right

*Schroeder* We do not know what changes occur when patients are active and subjected to everyday stresses

*Katz* Correct! This represents a first attempt to paint a broad picture

*Wakerlin* Would this statement apply to all parts of the body?

*Katz* Lamport probably would say that the limb flow is not changed as shown by temperature and plethysmographic measurements Abramson and I used the hand and foot plethysmograph and came to the conclusion that there might be some decreased flow in the muscles with an increased flow in the skin However the experimental errors are large and more definitive work must be done

With regard to the kidney flow one can say that the effective renal flow as measured by the present clearance methods with their known limitation is either unchanged or decreased in human essential hypertension Ultimately it is decreased Recently we completed a series of observations on changes in renal clearance values in hypertensive dogs during the course of about a year (16) We studied new and old nephrogenic hypertensive dogs also dogs spontaneously hypertensive for a period of two or three years (Figure 10) (16) The spontaneous hypertensive dogs all exhibited normal renal plasma flow and glomerular filtration rate This was true despite the fact that at autopsy we found slight to moderate focal renal pathology Serial renal clearances were done at intervals during their third year of known hypertension (Table VIII) There was no evidence that renal function was becoming progressively impaired in the face of prolonged hypertension Of the

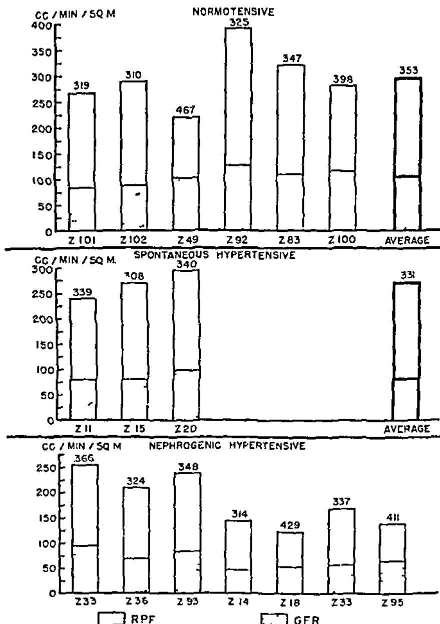



FIGURE 10 Average renal clearances in normotensive spontaneous hyperten sive and nephrogenic hypertensive dogs during approximately 1 year of observation RPF renal plasma flow GFP glomerular filtration rate these are represented by the height of the column from the 0 line The number at the top of the column is the filtration fraction (FF) All values are corrected to a surface area of 1 sq m

TABLE VIII

SERIAL RENAL CLEARANCES ON SPONTANEOUS HYPERTENSIVE DOGS

| Dog No | Time Interval After Initial Clearance Determination — Weeks | Glomerular Filtration Rate cc /min /M | Renal Plasma Flow cc /min /M² | Filtration Fraction % |
|---|---|---|---|---|
| Z11 | | 88 | 241 | 36.5 |
| | 4 | 84 | 275 | 30.6 |
| | 7 | 67 | 189 | 35.3 |
| | 39* | 84 | 225 | 37.4 |
| Z15 | | 79 | 222 | 35.6 |
| | 2 | 82 | 243 | 33.7 |
| | 10 | 82 | 280 | 29.3 |
| | 20 | 31 | 240 | 12.9 |
| | 28 | 78 | 300 | 26.0 |
| | 34* | 81 | 265 | 30.6 |
| Z20 | | 111 | 268 | 41.4 |
| | 5 | 100 | 281 | 35.6 |
| | 34 | 95 | 345 | 27.6 |
| | 40 | 116 | 300 | 38.7 |
| | 46 | | 290 | |
| | 64** | 57 | 267 | 21.3 |

*These clearances were done on the anesthetized animals using approximately 25 mg /kg of sodium pentobarbital

**5% sodium chloride solution was used as the intravenous hydrating medium in this clearance

nephrogenic hypertensive dogs some had normal kidney function others had significant depression of renal plasma flow and glomerular filtration with or without an elevated filtration fraction (Table IX) Among dogs with normal clearances some were recent others old hypertensives This was also true for animals with depressed clearances Serial determinations over the course of a year revealed no tendency for the renal plasma flow or glomerular filtration rate to increase or decrease with time

Since we have already had to concern ourselves with the role of anatomic vascular thickening in increased resistance to flow I want to point out that reduced renal blood flow in essential hypertension and canine nephrogenic hypertension cannot be attributed

TABLE IX

SERIAL RENAL CLEARANCES ON NEPHROGENIC HYPERTENSIVE DOGS

| Dog No | Time Interval After Bilateral Goldblatt Operation — Weeks | Glomerular Filtration Rate cc/min/M | Renal Plasma Flow cc/min/M | Filtration Fraction % |
|---|---|---|---|---|
| Z36 | 66 | 67 | 208 | 32 4 |
| | 68 | 75 | 218 | 34 6 |
| | 78 | 64 | 210 | 30 4 |
| | 102* | 62 | 216 | 29 0 |
| Z93 | 9 | 93 | 245 | 38 0 |
| | 32 | 56 | 260 | 21 5 |
| | 41 | 109 | 249 | 43 8 |
| | 62 | 84 | 301 | 27 9 |
| Z14 | 62 | 47 | 147 | 32 0 |
| | 77 | 37 | 119 | 31 1 |
| | 100 | 52 | 172 | 30 2 |
| | 120 | 48 | 172 | 27 9 |
| Z81 | 1½ | 41 | 121 | 33 9 |
| | 43 | 66 | 125 | 52 8 |
| | 49 | 54 | 141 | 38 3 |
| Z83 | preoperative control | 110 | 319 | 34 7 |
| | 4 | 53 | 185 | 28 8 |
| | 9 | 59 | 158 | 37 5 |
| Z95 | ½ | 61 | 140 | 15 7 |
| | 24 | 58 | 145 | 40 0 |
| | 37* | 71 | 168 | 42 3 |

These clearances were done on the anesthetized animals using approximately 25 mg kg of sodium pentobarbital

solely to fixed pathologic alterations in the blood vessels This is true even for the renal vascular bed in a Goldblatt dog with markedly reduced clearances There are dynamic factors operating The renin hypertensin system and other pressor systems as well may exert an effect We have evidence which fortifies this suggestion in some work on pyrogenic reactions in hypertensive dogs This is an extension of our previous work on the depressor effect of subcutaneous kidney implantation producing abscess (14) At one time I thought the depressor response was specific for the

kidney but my colleagues and I have come now to believe that it is a non specific pyrogenic reaction We have been able to reduplicate the results within the last year by using turpentine abscesses (17) We found we did get a sustained drop in blood pressure and we found under such circumstances that the renal flow increased even in Goldblatt dogs with markedly depressed renal clearances (Table X)

TABLE X

INCREASES IN RENAL PLASMA FLOW IN HYPERTENSIVE DOGS FOLLOWING TISSUE INJURY

| Dog No | Glomerular Filtration Rate cc /min /M | Renal Plasma Flow cc /min /M | Filtration Fraction |
|---|---|---|---|
| Z36 | 68 | 211 | 32 4 |
| | 74 | 293 | 25 4 |
| Z14a | 47 | 141 | 31 4 |
| | 55 | 404 | 13 5 |
| Z93a | 84 | 240 | 34 8 |
| | 84 | 378 | 22 2 |
| Z95 | 65 | 158 | 41 1 |
| | 85 | 304 | 28 0 |
| Z15 | 84 | 272 | 30 8 |
| | 80 | 343 | 23 4 |
| Z39 | 87 | 284 | 30 7 |
| | 89 | 374 | 23 8 |
| Z11b | 84 | 225 | 37 3 |
| | 92 | 304 | 30 3 |
| Z93c | 85 | 258 | 33 0 |
| | 109 | 249 | 43 8 |

One of the aspects of these results that interested us particularly was the demonstration that the decrease in renal blood flow in hypertensive dogs was reversible Of the several dogs in the series the greatest increment in renal blood flow was recorded in one or two Goldblatt hypertensive animals with markedly depressed control flows The most exciting thing to Dr Stamler Dr Rodbard and myself was to have new and longstanding Goldblatt hyper

tensive dogs with low control renal plasma flow exhibit a hyperemia' which in percent and on occasion in actual volume of flow was much greater than any hyperemia observed after abscess in spontaneous hypertensive dogs with normal control clearances and no constricted renal arteries The overall result was that at the height of the reaction the flow was more or less the same in all dogs significantly above the range we have recorded for normal effective renal blood flow in normotensive dogs Studies of the temporal and quantitative relationships between the drop in arterial blood pressure and the increase in effective renal flow lead us to conclude that the two phenomena are both the result of changes induced by abscess These changes humoral and/or nervous produce a generalized reduction in peripheral resistance including renal resistance *We do not believe the fall in blood* pressure can be ascribed to so called relief of renal ischemia We do believe that the increased renal blood flow demonstrates the dynamic element in the impaired renal hemodynamics of canine nephrogenic hypertension

We have also been making independent measurements of cardiac output in hypertensive dogs with the same chronic pyrogenic reactions In our initial studies we did cardiac outputs on anesthetized dogs and found the minute output was increased considerably during the depressor phase with abscess (15)

*Dexter* What anesthesia?

*Katz* Nembutal We are now extending these studies to the unanesthetized animal using a modification of the old direct puncture method of Marshall to determine cardiac output Our initial results suggest that the cardiac output is essentially unchanged or slightly elevated in the unanesthetized hypertensive dog during the depressor phase following tissue injury The whole point I was trying to make was this that apparently the drop in blood pressure cannot be ascribed to a decreased cardiac output

*Dexter* That is right

*Katz* Whether my values are quantitatively precise or not they demonstrate that the cardiac output strives to compensate for the marked fall in peripheral resistance

*Ogden* You made the point that you found the same amount

of blood leaving the heart and also that the coronaries are probably taking more of it. Where is the deficit?

By the process of elimination you came to the experimental evidence suggesting that the kidneys are the ones that are taking less. That is not entirely surprising in view of the fact that the resting kidney takes an enormous proportion of the blood, probably more than it needs. You can cut down the kidney blood flow without producing any other measurable changes. You might say that somewhat like the venous and splanchnic reservoirs, the renal circulation is a part of a flow reserve like a motor idling rapidly to get away quickly in traffic. When you place a Goldblatt clamp on the kidney, and sometime later by inducing a pyrogenic reaction in the animal increase the flow to the kidney, you are spotlighting a fact which should be given considerable emphasis. That is the fact that the Goldblatt clamp is not the limiting factor in the flow. The clamp is producing an effect other than that which we think it is doing, something perhaps affecting the blood pressure. You certainly are not getting your abscesses to unscrew the renal artery clamp for you. This represents a further piece of evidence to help throw out the horrible phrase, ischemic hypertension.

*Katz*: Thank you very much for your excellent analysis.

*Fremont-Smith*: Are you willing to say, Dr. Katz, that if we assume there is arterial constriction, that all the rest of what we know happens would follow?

*Katz*: In a broad sense, yes.

*Fremont-Smith*: That was one impression I received. The other is the possibility of redistribution of the blood flow. May I call your attention to studies performed by Mendelsohn in Conheim's laboratory and published in the American Journal of Medical Science in 1883. Conheim, using dogs, produced experimental fever by intravenous injections of pepsin. The kidney was placed in Roy's oncometer to measure blood flow. He showed that as the fever rose there was a sharp decrease in kidney volume that could not be attributed to any change in blood pressure. These experiments were not done under anesthesia because Mendelsohn noted that he could not produce fever in anesthetized animals. He devised what was probably equivalent to a decerebrate preparation by what he called thalamic puncture. After this procedure he reported their dogs lay quietly without anesthesia. I mention this experiment

which seems to have been carefully performed since I believe it to be the earliest clear cut experiment indicating diminution of blood flow through the kidney as the result of active vasoconstriction

*Katz* Apropos of Dr Dexter s statement while our initial cardiac output experiments were carried out in the anesthetized animal our renal clearances were all done in trained unanesthetized dogs

*Wakerlin* I think it is important to determine whether even a slight degree of renal ischemia is necessary for the production of experimental renal hypertension I wonder if in any of your dogs you have run PAH clearances before and after renal artery constriction

*Katz* *All our renal plasma flow determinations were done* with PAH We have clearance values prior to and following the Goldblatt operation in a few dogs All of the animals in this group exhibited a significant decrease in renal flow after operation Unfortunately we have no preoperative control data on dogs with persistent renal hypertension who repeatedly exhibited postoperative clearance values well within the range of normal e g dogs Z36 and Z93 Our data clearly show however that the renal clearances do not change with time in spontaneous or Goldblatt hypertensive dogs whether the flow in the latter was normal or depressed in the early postoperative period

*Wakerlin* The only work I know is that of Dr Page and associates and of Dr Thomas They studied a small number of dogs I think even one dog if the renal blood flow remained normal would indicate that renal ischemia is not necessary for the production of renal hypertension We ought to have a good series of dogs in which we have enough determinations of renal blood flow so that the normal range for each normotensive dog is known before renal artery constriction In the dogs previously reported as showing no change in renal blood flow (even though the animals were hypertensive) there might have been a small decrease It is a very important point to settle It is amazing that after so many years we do not yet know whether or not renal ischemia is necessary for the production of experimental renal hypertension

*Goldblatt* I might interject one thing Unfortunately there is no common understanding about what is meant by ischemia

When I first used the term I wished to denote a disturbance of the circulation probably involving a reduction of blood flow through an organ It seemed logical that considerable reduction of the diameter of a tube would decrease outflow beyond the site of constriction That did not exclude a change of pressure beyond the clamp or altered pulsation of the kidney itself which has been referred to as altered pulse pressure What I did hope was that by means of the clamp on the main renal artery a circulatory disturbance would result inside of the kidney similar to the effect of renal obliterative arterial and arteriolar sclerosis I think we should come to a common understanding about what we mean by the term ischemia

The other matter is the question whether one can determine by indirect methods the slight changes of the blood flow through the kidney which might cause significant disturbance of blood pressure

*Wakerlin* I think it is important that we make a serious attempt at doing it Dr Goldblatt We all agree there is some alteration in renal hemodynamics produced by renal artery constriction The question is whether it involves a mild degree of ischemia or none at all I don t think we have as yet the answer As far as I know we also don t have the answer as to what happens to the diastolic and systolic pressures in the renal artery beyond the clamp in the *chronic* hypertensive dog If someone has the answer I would appreciate hearing about it

*Schroeder* Blalock did some experiments in that regard

*Wakerlin* His experiments involved clamps left in place for only a few days I am talking about weeks or months not a few days It has not been done so far as I know

*Katz* Just to fortify your point without necessarily supporting it even if there were no change in renal flow you would not be able to say that certain parts of the kidney did not have diminished flow?

*Goldblatt* One cannot say that

*Ogden* I think a good deal of this argument results from people who read your words redefine ischemia to fit their own ideas and then create an apparent discrepancy Did not Herrick report several hypertensive dogs with no decrease in flow measured?

*Page* I was not aware that any measurements of renal blood flow were made except after angiotonin Corcoran and I used clearance methods finding normal values in many cases with hypertension whether produced by clamps or perinephritis We felt that this represented another similarity between experimental and renal hypertension It seems to me that we should keep to the simple definition of ischemia given by the dictionary namely, local diminution in blood supply It is our impression that pulsation of the kidney is a more important factor than ischemia in the initiation of hypertension

*Grimson* Dr Katz made a statement when he came to the moderator compensation mechanism that it was normal in the hypertensive patient He meant by that that the carotid sinus was operating, that blood pressure could be increased or decreased by increasing or decreasing the pressure in the carotid sinus Isn t it possible nevertheless that the moderator mechanism or the cardio aortic and carotid sinus buffer nerve mechanism might be working abnormally in the hypertensive patient otherwise you would have no hypertension? Normally it is set to regulate blood pressure at a level of 120 and at least this must happen it is readjusted at a much higher level Whether that change be primary or secondary as a cause of hypertension is not known

*Katz* The question remains whether there is an increase in buffer mechanism activity in hypertension I would answer that with *No* The point you make is valid namely that in a hyper tensive person the moderator response to acute pressure changes is the same as the normal Therefore the moderator mechanism operates the same only the differential manometer is set at a higher level I would be willing to concede that in the pre hyper tensive state an unbalancing of the moderator mechanism might result in a given stress producing a longer and more severe hyper tension To oversimplify again such a situation might leave a residue in the musculature of the arterioles If you take that as one factor and the other the number of times one gets emotionally wrought up the product might be pathogenetically significant I am easily wrought up but since I am an extrovert I dissipate the energy Those of you who are repressing your hostilities may be setting up mechanisms for blood pressure elevations

*Ba ett* I would like to raise the question of size against resistance or conductance I personally would like some expression

from this group on this question It does not seem possible to relate flow to the kidney to surface area If you wish to relate to size in general possibly mere weight is the simplest to use

If you take the two kidneys with a weight of approximately 0 3 kilo and a flow of about 21 ml per sec their absolute resistance at a mean pressure of 90 mm would be 4 3 R units and their conductance is the reciprocal of this The muscle mass in the same sized individual would have a weight of about 31 kilograms with a flow of 14 ml per sec and a resistance of about 6 4 R units Though the absolute resistances are similar the resistances calculated relative to the flow per kilogram would differ enormously I should like to express resistances relative to size as resistance kilogram units so they would be Kg R units where the flow is estimated as the flow per kilogram rather than flow absolute Then the relative resistance of the kidneys becomes 1 3 and that of the muscle masses as 198 Kg P units It seems to me this represents better the difference between the muscle and the kidney at rest Also in an individual who goes into shock and has to constrict in order to maintain his pressure he cannot further constrict tissue that is only getting 14 cc per second for 31 kg In the kidney he can induce an enormous change so that it is obvious you must change this low resistance and not the high relative value if pressure must be maintained On physical principles the liver and kidney have to constrict in such a real emergency However if this constriction is maintained then the liver and kidney may be damaged irreversibly It seems to me it makes a logical story I do not know whether it is better to use resistances or conductances in thus considering the effect of size But size cannot be neglected For instance if you take the resistance of a child of three years the absolute resistance is much higher than that of a hypertensive man The conductance in a child of three years is a lot lower than the conductance of a hypertensive man You must have measurements with a size factor if you are going to make cross comparisons It seems to me it would be useful to get some idea how you would do it I do not want this factor to be forgotten

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*Goldblatt* Dr Lamport will now deal with an analysis of renal hemodynamics

# AN ANALYSIS OF THE HEMODYNAMICS OF THE RENAL CIRCULATION


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I may have trespassed somewhat on Dr Katz realm of the systemic circulation I hope Dr Katz will forgive me if I remark that there has been some reciprocation he already has made several excursions into renal territory

This diagram (Fig 11) at first glance appears somewhat confusing I will however try to show you another way in which to view the kidney First let us confine our attention to the left hand portion (Fig 11 A) The reason for bringing this figure to your attention is to analyze the question raised by Trueta and his co workers (23) as to whether or not there is a diversion of blood from the cortex of the kidney by the so called renal shunt That has already been alluded to in the discussion by Dr Katz of possible diversion of blood by a shunt You will notice the blood goes through the renal arteries and its branches the arcuate and the

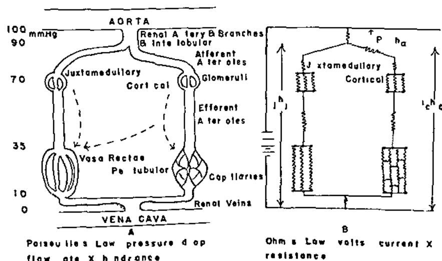



FIGURE 11

interlobular Then there is a separation some blood going through afferent arterioles supplying the juxtamedullary glomeruli while the rest supplies a parallel circuit through cortical glomeruli After emerging from the efferent arterioles the capillaries about the tubular convolutions or the vasa rectae are supplied, if the anatomical descriptions of Trueta are accepted Finally the shunting pathways reunite in the renal veins which drain into the vena cava (The dotted lines indicate the routes of glomerular filtrate before it is reabsorbed in the capillaries )

I shall use the word hindrance for reasons already mentioned to characterize the opposition of a system of vessels of given dimensions to the flow of blood through them For lack of good symbols in hemodynamics I have simply translated the hemodynamic terms of pressure flow and hindrance into the corresponding electrical terms of potential current and resistance because we have in electricity a shorthand that I find convenient to use I have translated Fig 11 A into Fig 11 B so that I can use Ohm s law the electrical analog of Poiseuille s law It may seem strange to you that I am using Poiseuille s law as a point of departure for analyzing renal blood flow not long after I got through explaining that in the body blood does not obey Poiseuille s law Poiseuille s law may be used as an approximation particularly where the flow rates are high as they are in the kidney, where the blood pressure is not subnormal and where an approximate result an order of magnitude suffices All these requirements are met I believe in the application I am here making

I have broken up the pressure drop as we go down the vascular path from the aorta using Ohm s law volts equal current times resistance The pressure drop is equal to current multiplied by the resistance which I have labelled $h_a$ in the portion between aorta and the point in the interlobular arteries where blood branches off to juxtamedullary glomeruli From this point down to the vena cava is the remaining portion of the circuit labelled as shown in Fig 11 B We can analyze this last pressure drop in terms of either the juxtamedullary or cortical glomeruli route That is one of Kirchoff s laws in electricity It applies perfectly well for fluids obeying Poiseuille s law

From this point on my analysis will be mathematical * I am

The oral presentation of this analysis of renal blood flow is not definitive A contribution on this subject which presents the author s views in definitive form is to be published elsewhere

not certain that it will be old fashioned reasoning from here on but I hope so Pelying on the partition of pressure (or voltage) in Fig 11 B we have

$$100 = P + i\,h = ih_a + i_c h = (i + i_j)h + i\,h_c$$

Solving for i

$$i = \frac{100 - i_j h}{h + h_c}$$

And we now have a formula which may be useful since i is the flow rate through cortical glomeruli with the pressure of 100

Our question is phrased this way what is the effect on i the flow through cortical glomeruli of changing the juxtamedullary flow $i_j$? If $i_j$ goes to a new value $i_j$ everything else unchanged only the vessels in the juxtamedullary portion shifting what is the effect on i which becomes i ? We shall evaluate our expression for i As you recall h is the arterial portion (Fig 11 B) which the two sections of the kidney have in common and it is a constant Accordingly we can evaluate it under any conditions we choose Under normal conditions let us call the values of P and i P and i We therefore see that h = P /i

Returning to our formula

$$i = \frac{100 - P\,i_j/i}{h + h}$$

and

$$i = \frac{100 - P\,i_j/i}{h + h}$$

Or

$$\frac{i}{i} = \frac{100 - P\,i_j/i}{100 - P\,i_j/i}$$

Now in order to throw all the cards in favor of the hypothesis of a significant renal shunt let us choose such circumstances as will make this change as great as possible because in that way we will know what the greatest conceivable change can be When i /i is smallest the greatest diversion of blood from the cortex results from the shunt $i_j/i$ is smallest when $i_j/i$ is largest Correspondingly in the denominator we must at the start set $i_j/i$ as small as possible to make the largest denominator The

smallest value we can use to accomplish our purpose is to set $i_j/i$ equal to zero That corresponds to saying that the original amount of blood going through the juxtamedullary glomeruli is almost nil so that we have chosen the most extreme position to favor the hypothetical shunt

We will also take a very extreme position for $i'_j$ We assume that dilation is so great that practically all of the blood going through the juxtamedullary glomeruli during the shunting phenomenon is as much as originally went through the whole kidney No more favorable choice in terms of the shunt can be made Since $i$ is the original flow value for the whole kidney we assume that the ratio is $i'_j/i$ is almost 1

The expression for $i_c/i$ now simplifies since $i_j/i \longrightarrow 0$, $i'_j/i \longrightarrow 1$

$$\frac{i}{i_c} > \frac{100 - P}{100}$$

and where $i - i \simeq \Delta i$

$$\frac{\Delta i}{i} < \frac{P}{100} \approx 10\%$$

We have chosen a generous value for P of 10 mm Hg which indicates that the juxtamedullary glomeruli by starting tightly constricted and dilating maximally cannot divert more than 10% of the blood flowing through cortical glomeruli The converse applies equally well constriction of the medullary vessels will not in itself augment cortical flow by more than 11% It therefore seems unlikely that the so called renal shunt is an important hemodynamic mechanism

The physiological function of these juxtamedullary glomeruli has already been touched on In Detroit at the Federation meeting of the Circulatory Section evidence was presented to show that the renal extraction ratio was not changed materially under rather stringent physiological and some pathological conditions so that we are left I think with the position that we do not have significant diversion of blood between cortical and juxtamedullary glomeruli and that both groups appear to filter and secrete similarly

*Bywaters* Does that take into account the different numbers of juxtamedullary and purely cortical glomeruli?

*Lamport* Yes it does If you recall I have made no statement here about the size of $i_j$ except when I weighted it in favor of the hypothesis

*Kety* It seems to me your derivation has been based on the assumption that the cortical nephron itself does not have any regulatory influence This is simply an effect upon the cortical nephron flow when the other shunts open or close Isn t it possible that the cortical nephron itself may clamp down in which case a much greater than 10 percent change could occur in its flow

*Lamport* I have found it possible to interchange the words cortical and juxtamedullary throughout the derivation Then one concludes that juxtamedullary flow is not affected by more than 11% when cortical flow is reduced most severely and that augmentation in the juxtamedullary glomeruli after maximal cortical dilation is no more than 13% at the very most Actually these figures are exaggerated because of our generosity in favoring the hypothesis so extremely

*Ogden* Can you assume that blood can go through either with equal ease? If there is no selective constriction you have the same number of cortical and juxtamedullary glomeruli and they have the same resistances?

*Lamport* What I have done here is to handle an artificial but representative system I am replacing all the cortical glomeruli by a single glomerulus and all the juxtamedullary glomeruli by a single one and then I ascribe to each of them a hindrance which will give a partition of flow corresponding to the physiological facts I do not know what the actual proportion is I make only those assumptions about the proportion of blood flowing through these regions as will most favor the shunting mechanism

*Ogden* You estimate the limit of the hindrances to be 1 Isn t that making an assumption about the aggregate cross sectional area you want of those two things? It is quite conceivable even though there are relatively few of the juxtamedullary ones they may have individually a very low hindrance Therefore that figure might be greater than 1

*Lamport* It is possible Parenthetically may I say I originally evaluated this question in terms of numbers using the rabbit I found it too complicated mathematically to explain freely here If you take 15 percent of all glomeruli which is the value in the

rabbit quoted by Trueta for the juxtamedullary glomeruli (23), you find that 15 percent of the glomeruli of the kidney now have to pass the normal amount of renal blood for the ratio of $r_j/r$ to be 1 That is roughly a seven and one half times increase from the average flow rate so already we are going very far in our concessions to the hypothesis The range of renal flow that Homer Smith has used in his study of ischemia and hyperemia is two to one in other words a drop of 50% on the one hand and an increase of 200 percent on the other so I feel a seven and one half fold increase is very generous (22) However if we interchange cortical and juxtamedullary in our derivation, the ratio of $r/r$ may possibly be placed as high as 1 25 in detecting the effects of cortical dilatation since Pappenheimer and Maes found hindrance decreased by about 25% after denervation (19) The result is 12½% no doubt a gross exaggeration of the possible juxtamedullary shunting effect of cortical dilation

*Katz* Did you not in your first slide say that Poiseuille's law was Newtonian? I heard you say here it is not Newtonian

*Lamport* Poiseuille s law does not apply quite properly but all laws are approximate as I look at it The field of application and the precision required determine our choice In other words Newton s laws are correct as an approximation until velocities approach light when Einstein s laws supercede them Here we are trying to study a very gross effect and if we were to use instead of Poiseuille s law a more precise one we would get a result very similar to this because the small changes would be minor in comparison with the gross effect being considered

*Schroeder* Are you assuming that if a leak occurs in the glomeruli the resistance is unaffected? There must be an electrical leak in the system between the resistances which would be analogous to glomerular filtrate Because of concentration of blood in the efferent arteriole the resistance is going to be higher This may give added weight to the difference between afferent and efferent

*Lamport* In view of the fact that no difference in function in terms of extraction ratio had been found it seemed to me reasonable to treat the juxtamedullary glomeruli and the cortical ones as roughly equal in function It is true there may be some difference but notice our attention has been limited to blood flow not to elaboration of urine If you take the efferent arteriolar por

tion of the circuit which is not a very great portion there is an offsetting factor to the loss of filtered fluid As blood goes through the glomeruli it is concentrated it is reduced in volume but another factor is hemodynamically offsetting the loss of filtrate increases the viscosity of the remaining blood The decreased volume and the increased viscosity have contrary effects which tend to cancel one another With a filtration fraction of 30 percent as I recall it the error by neglecting it completely is around 12 per cent (10)

So again I feel that these corrections are trivial compared to the gross weighting of the scales in favor of the shunt In the end despite our travail on behalf of the shunt we were unable to squeeze more than a 13% shunting effect on a purely hemodynamic basis

*Schroeder* It may be of some interest that we found the greatest change in the extraction ratios after the administration of epinephrine was 11 percent

*Kety* With an aneurysm of the brain where you have a tremendous AV shunt the blood flow to the rest of the tissue does not become seriously restricted In the extremities the same situation applies

*Lamport* We see this effect in electricity all the time If you have a good power line your lights are not dimmed when your neighbor turns his on If they are dimmed it is because the line is too small In the kidney it happens the power lines (arteries) are very big where the juxtamedullary and cortical supplies separate

*Goldblatt* Dr Ballard would like to speak to the point under discussion?

*Ballard* I hesitate to say anything because I am completely out of my medium being an electrical engineer knowing nothing about medicine The application of Ohm s law to the case of the hydraulic system is something we in engineering would like to do very much However we are not able to do it because it introduces a large percentage of error because this term used hindrance is a function of the flow rate a function of pressure applied Any development that assumes hindrance is a constant value for the entire series is to be taken with some question as it will introduce considerable errors I think the speaker has already

pointed out this is only an approximation The percentage error might be anywhere from two to twenty, depending upon the actual variation in the hindrance

*Lamport* What Professor Ballard is referring to, I believe is the study of turbulent flow of water through large pipes But in the kidney we are dealing with tiny hair like tubes and we do not have turbulence

*Dexter* Can you tell us why under certain conditions Trueta can apparently produce bilateral cortical necrosis of the kidney?

*Lamport* That might be a direct phenomenon due to vaso constriction I am not inferring that vasoconstriction in the cortex does not exist I say the reciprocal effects of juxtamedullary or cortical vascular changes on one another are not significant hemo dynamically *Observed differences between the two regions must* result from other causes

*Goldblatt* This is important There may be patchy or even diffuse vasoconstriction and ischemia in the cortex that is not on the basis of the medullary shunt or by pass of Trueta and collabo rators

*Lamport* Words are very useful tools but they can also be seductive I think shunt and 'diversion have been the pitfalls It is when we put quantitation in qualitative ideas that we may discover that the qualitative ideas are unsound At least that is my view of the so-called renal shunt

* * *

Figure 12 is frankly speculative I am bringing it before you to hear your reaction to it I am attempting to implement and refine to some small extent an idea which appeared in a paper by Kohlstaedt and Page (9) and of which Dr Ogden has been a pro ponent (18) On the basis of a perfusion experiment Kohlstaedt and Page suggested that a reduction of arterial pressure pulse in the kidney may be responsible for renin formation My considera tion of this observation does not mean that I subscribe to their view I do feel that there is a significant feature related to pulsation

The left hand column presents a view of normotension We have 100 mm Hg pressure going to zero by way of hindrances leading to the glomerulus then the efferent arterioles the capil laries and venous system This is just a crude picture using the

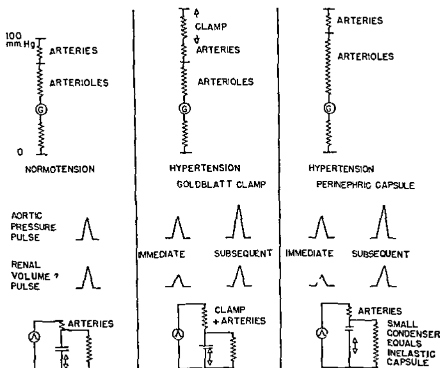



FIGURE 12

same electrical symbols as in Fig 11 B for ease of description of pressure and hindrance relationships The small bar at the high pressure side of the diagram demarcates a separation between arteries and arterioles At the bottom of the column I have drawn what I think may be an electrical circuit analogy to the condition in the kidney an electrical analogy here again for the same reason as before because we do not have a good chirography of our own for representing these things

I have put in a pulse generator the V shaped symbol in a small circle It produces simple saw tooth shaped impulses It corresponds roughly to the pressure pulse of the arterial blood which I have indicated in the second row in Fig 12 Below it is the corresponding volume-pulse I do not think the pressure pulse is of primary importance in the kidney I am not certain that the volume pulse is that is why I have placed a question mark next to

it *But corresponding to the volume pulse there is probably some tidal flow of tissue fluid about renal cells which affects their activity* Thinking about the nutrition of the kidney and perhaps other organs has usually started and ended with the word 'ischemia' I believe the primary phenomenon has to do with the nutrition or rather metabolism of the single cell The metabolism of the single cell is in some way related to the tidal flow of tissue fluid around it Hence if you consider the volume pulse you will not be too far removed from the question of how well the single cell is being nourished and how well its catabolic products are being removed Here in the left column of Fig 12 corresponding to the pressure pulse in the normal kidney I have drawn some kind of volume pulse which for the sake of argument, we shall consider normal

The volume pulse comes in large part from the arteries because as we know the pressure pulse is largely damped out by arterioles as Dr Zweifach mentioned this morning That is why I placed the bar in the uppermost row of Fig 12 to indicate the transition from arteries to arterioles For the same reason the condensers in the lowest row are connected at the corresponding point of transition The condenser represents the volume elasticity of the kidney the ease with which it expands in an oncomotor We are forced to use the macroscopic volume pulse of the whole organ as representative of the microscopic tidal flow about single cells for lack of better knowledge of the microscopic phenomenon

Corresponding to the volume pulse there is tidal flow in and out of the condensers which I indicate by the double tipped arrow I hypothesize that this tidal flow is related to a normal maintenance of blood pressure

In the middle column of Fig 12 we illustrate renal hypertension produced by the Goldblatt clamp The pressure drop across the hindrance which the clamp has introduced roughly corresponds to the elevation of blood pressure above the normal level I have crudely indicated in the lowermost diagram which represents the subsequent status that the basic potential is higher than it was before although the potential across the condenser is represented as about the same as in the normal case The size of the condenser is *also the same When the clamp is placed on the renal artery* it seems to me the kidney is about the same as it was before in terms of elasticity but the increase in extra renal hindrance caused by

the clamp interferes with the tidal pulsation of tissue fluid in the kidney I hypothesize that the immediate effect of constricting the clamp is a diminution of renal pressure and volume pulse The electrical expert would say that the time constant is too long because of the increase in the electrical resistance through which the condenser is pulsatively charged I suggest that there may be some homeostatic renal mechanism related to volume pulse or whatever cognate phenomenon such as intercellular tide it may be and that as a consequence systemic hypertension develops As Dr Katz remarked hypertension is associated with increased pulse pressure the effect of which would be to restore the renal volume pulse nearer to normal despite the damping effect of the constrictive clamp The figure shows the conjectured change in aortic pulse pressure and renal volume pulse

Let us now go on to the hypertension produced by some type of perinephric capsule such as cellophane which Dr Page and others have worked with The right hand column in Fig 12 shows this case with the arterioles doing the major work of sparing the glomeruli from increased pressure The immediate effect again we believe to be a reduced volume pulse due to a rigid capsule The rigid capsule corresponds to a small condenser one requiring the flow into it of a smaller charge to reach a given potential difference and that we have indicated by a condenser with smaller plates compared to the normal ones already discussed Arterial hindrance has been presumed normal What will happen? I suggest a small volume pulse is the immediate result due to the inelasticity—the small condenser Subsequently the homeostatic mechanism produces high blood pressure with a high aortic pulse pressure And normal renal pulsation due to the increase in the size of the pulse pressure results despite the inelasticity of the kidney

*Schroeder* It still seems to me that the leak which would be glomerular filtrate may produce profound changes in flow beyond the efferent arteriole Of course the difference in resistance between afferent and efferent (that is the pressure in the glomerulus) is extremely important to maintain this leak

May I get back to a hydraulic system If we set up a constant pulsating pressure put 2 clamps with a segment of tubing between and measure the outflow from the system we can readily demonstrate that constriction of the proximal clamp profoundly

affects both flow and pressure distally when we do not alter the distal clamp On the other hand pressure in the segment can be maintained at the expense of flow providing the distal clamp is tightened Likewise flow through the system can be maintained at normal levels by opening the distal clamp but at the expense of pressure in the segment If you make a pin hole in the tubing of the segment and allow a leak tightening the proximal clamp will produce much more profound changes upon either pressure or flow than before In other words the presence of glomerular filtrate profoundly modifies the changes in pressure and flow through the system which can be produced by the alteration of either afferent or efferent arterioles

*Lamport* In the glomerulus we have no evidence of pulsation in the capillaries Since we are considering here the pulsation in the kidney it is of no real importance whether we have a fluid pathway outside blood vessels through peritubular apertures and through nephron tubules or whether it is through blood vessels Such pathways simply become a portion of the post glomerular electrical resistance How it is distributed anatomically is not vital to our hypothesis When considering pulsation we must consider a source of varying potential superimposed on the steady potential delivered by the battery It is the signal generator in Fig 12 not the battery of Fig 11 which is significant

*Bradley* Another point in pulsation is the volume of regurgitation With each pulse blood flows forward and back again Hence when you place a blood pressure cuff on an arm above the diastolic pressures you find that the mean pressure rises distal to the cuff

*Lamport* But the degree of pulsation has been reduced

*Schroeder* If the needle of a Hamilton manometer is placed in the artery distal to a cuff and the cuff is inflated to diastolic levels both the systolic and diastolic pressure beyond the cuff will be elevated This is known as the breaker phenomenon It was first described by Erlanger in 1916 and later studied by Bramwell in 1925 The systolic elevation is due to a steepening of the wave front and the diastolic caused by obliteration of regurgitant flow

*Bradley* You sometimes get it It depends upon the degree of filling in the system distal to the cuff

*Lamport* It depends upon reflection flow rate as well as how much of a constriction you have With a large constriction you will have a great deal of damping If you take a Hamilton manometer and interpose resistance between the manometer and needle you find it acts like a dampened system and you lose pulsations

*Katz* I would first of all like to support your electrical analogy One of my former associates Kenneth Jochim has actually used that not in relation to the kidney but simply as an analogy for the whole circulation Another pulse which I have studied is the velocity pulse Could it be that the volume pulse is unimportant and that it is the velocity pulse in millimeters per second which is important?

*Lamport* The two may be related I put a question mark opposite volume pulse just for that reason I feel in my own mind I am admittedly groping here it might be some other factor

*Katz* The only reason I introduced velocity pulse measurements with flow methods is that they show a negative wave occurring at the end of systole in the carotid artery

*Fremont Smith* We should consider elongation of the arterial tree within the kidney which also will exhibit pulsations with each systole

*Ogden* The fluid enters the kidney through the artery and gets out in part through the vein and in part through the ureter and in part through the lymphatic channel It is not inconceivable that the outflow of fluid from the kidney is helped by the movement similar to the massaging action of the muscle movements in the extremities If the outflow is slowed up in the absence of pulsation fluid might accumulate interstitially thereby requiring more time for oxygen and other substances to diffuse from the vascular system to the cells which become hypoxic or ischemic

*Katz* It might form the framework for a working hypothesis

*Lamport* While we are speculating I would like to carry the speculation one point further by turning our attention back to juxtamedullary glomeruli As you know the vasa rectae form a blood vascular capillary loop supplied by the efferent arterioles of the juxtamedullary glomeruli and draining into venules tributary to the interlobular veins The loop formed by the vasa

rectae is quite similar in location, orientation and configuration to the loop of Henle, with which it is clearly associated Thus the vasa rectae are straight vessels, whence their name which means "straight They are directed radially with blood in the arterial arm flowing centrally in the same direction as that in the interlobular veins The blood in the venous arm of the vasa rectae flows cortically in the same direction as the pulse wave propagated at each heart beat through the renal and arcuate arteries and then radially towards the cortex in the interlobular arteries

*Goldblatt* I challenge definitely the idea that there is an arcuate artery I don t think there is Dr L Gross showed many years ago that in no animal including man is there such a thing as a true arcuate artery There is very early a branching of the renal artery intrarenally These individual branches now form interlobular branches and the remainder of the vessel which you are discussing I don t believe that there is reason to perpetuate the idea of an arcuate artery in the way you have depicted it

*Lamport* This does not change the argument It actually aids it The arterial pulsation starts at the hilum of the kidney in the large branches of the renal artery and travels towards the periphery of the kidney We can well see how such a pulse wave as it traveled peripherally associated with a volume pulse might have important hemodynamic and tissue fluid dynamic implications The long straight radial vessels of the vasa rectae and the long straight tubes of the loop of Henle are most likely to be affected by such a radially directed pulsation The pulsation may have a milking effect on these straight tubes particularly on the venous arm of the vasa rectae The possibility of tidal flow associated with renal volume pulse being significant in the etiology of hypertension has already been mentioned

At last year s Conference Dr Selye stated that in the so-called endocrine kidney which essentially is a Goldblatt kidney with the ureter tied off there is an increase in the importance of the vasa rectae whether it is hypertrophy or hyperplasia is not clear The fact that in a form of renal hypertension the vasa rectae become very prominent would suggest that this zone may be vital in controlling blood pressure levels in this entity

* * *

Now I will turn to my last topic Is filtration equilibrium reached in the glomerulus?

The psychological basis for our belief that filtration equilibrium is reached in the glomerulus derives I think from our desire to have it achieved there Certainly, the kidney is a much simpler organ to draw conclusions about if we can assume filtration equilibrium is achieved in the glomerulus (10 22 12) I do not mean to imply equilibrium is not reached in the glomerulus but I want to cast doubt on our basis for concluding that it is

*Bywaters* Might I ask what you mean by filtration equilibrium?

*Lamport* By filtration equilibrium I mean the condition when osmotic pressure and net hydrostatic pressure across the glomerular capillary wall are approximately equal before the blood leaves the glomerulus Equality is approached asymptotically it would take infinite time to reach equality

*Fremont Smith* Would it be correct to say If the glomerular capillaries were elongated no further filtration would take place ?

*Lamport* That is perfectly stated The basis for the belief that filtration equilibrium is reached in the glomerulus derives I think primarily from Homer Smith who with his co workers studied creatinine and inulin and other clearances (22) They found that in the dog creatinine and inulin clearances are substantially equal and measure the glomerular filtration rate I hope no one will misunderstand our argument and carry away the idea that doubt has been cast on the validity of the clearance method for measuring glomerular filtration rate

The next fact brought forward in the argument is that the diffusion coefficient of creatinine is 4 8 times that of inulin when tested in water (3) That means that inulin is a slowly diffusing molecule and creatinine is a rapid one Smith and his collaborators then go on to conclude since the two substances are cleared at approximately the same rates despite their considerable difference in diffusion coefficients that filtration equilibrium is very likely to have been reached Otherwise they would have expected that the slower diffusing inulin should not have been cleared so quickly as the faster creatinine

I pose the question Does equality of filtration rate of differently diffusing solutes indicate filtration equilibrium? A way to answer this question is to translate it into another question What discrepancy between inulin and creatinine clearances is to be ex

pected if filtration equilibrium is *not* reached? By answering this question we can determine how wide a deviation from filtration equilibrium is consistent with the precision of the experimentally observed equality of the clearances In seeking to answer this question I have had to develop differential equations for diffusion across the glomerular capillary membranes I am not altogether certain that the application in the first instance is correct That is the place where applied mathematics often fails in the original application of equations to the physical problem *

Let us consider a representative single glomerulus in man with blood of a 50 per cent hematocrit and an osmotic pressure of 24 mm of mercury Table XI refers to a single glomerulus and sets forth estimated facts concerning this glomerulus

The volume of the glomerulus capillaries given in Table XI is roughly 80 to 85 per cent of the volume of the glomerulus The linear velocity of the blood in glomerular capillaries is about 2 0 mm per second This figure is not used in our analysis I inserted it as a matter of interest The linear velocity of blood flow for the retina one of the highest in the body is about 0 9 mm per second Our estimate suggests that blood is flowing very quickly (linearly) through the glomerular capillary

The pressure drop in the glomerulus I estimate to be less than 2 mm of mercury This estimation is a difficult one because it depends on the estimated diameter of the capillary which is not

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Since the Conference at which I intimated that the mathematical application of the laws of diffusion there reported might be incorrect I have concluded that such was indeed the case The method followed was to compare the maximal difference in clearance between inulin and creatinine assuming diffusion alone caused these solutes to appear in the filtrate This is a very conservative hypothesis in that it grossly overestimates the maximal difference in the *two* clearances Despite this conservatism the maximal difference it will be seen later is less than 1% irrespective of the degree of filtration equilibrium achieved (within physiological limits) For this reason the method followed here is none the less worthy of attention since it indicates that even the heaviest weighting of the scales in favor of the use of clearance differences for determining the degree of filtration equilibrium does not rescue it from the defect of indeterminateness

The point raised later by Dr Kety appears to be quite correct inulin and creatinine are carried across the semipermeable glomerular capillary membrane by the filtered water by the process of convection which far outweighs diffusion as a factor The value of the approach resting on diffusion alone which I follow here is that the force of the argument for convection is not immediately apparent to many of us — witness the discussion of it below — so that the quantitation offered here is helpful in proving the unsoundness of the most extreme form of the argument advancing the importance of the identity of inulin and creatinine clearances

TABLE XI

ESTIMATED FACTS CONCERNING A SINGLE REPRESENTATIVE GLOMERULUS IN NORMAL MAN

| | |
|---|---|
| Total number both kidneys | 2 000 000 |
| Blood flow rate | $12 \times 10^{-6}$ cc /sec |
| Volume of capillaries | 0 0030 $mm^3$ |
| Circulation time | 0 25 seconds |
| Average linear velocity of blood flow | 2 0 mm /sec |
| Blood pressure drop | < 2 mm Hg |
| Diameter of representative capillary lumen | 16 micra |
| Effective thickness of wall of representative capillary | 2 micra |
| Diffusion coefficient for inulin across capillary wall | 0 61 cm /min |
| Plasma filtration fraction | 20% |
| Osmotic pressure of blood in afferent arteriole | 24 mm Hg |
| Osmotic pressure of blood in efferent arteriole | 30 mm Hg |
| Net hydrostatic pressure corresponding to 95% filtration equilibrium | 31 6 mm Hg |
| Net hydrostatic pressure corresponding to 50% filtration equilibrium | 60 mm Hg |

precisely known I have chosen for the diameter of the capillaries 16 micra In the physiological literature I find a capillary lumen that is double this in size (1) I have purposely chosen the smaller value in estimating glomerular pressure drop if it were larger the pressure drop becomes much smaller practically zero Even with 16 mu estimated bore which is approximately twice the diameter of a red cell we obtain a pressure drop of less than 2 mm of mercury

The diffusion coefficient for inulin was measured by Bunim Smith and Smith *in vitro* (3) We apply this figure to the capillary

wall estimating the capillary wall to be equivalent in diffusion characteristics to water 2 mu thick This application is subject to objection The capillary wall including the epithelium on the outside of the capillaries, appears less than 2 mu thick Homer Smith in one of his papers estimates the thickness as one mu (22) However the greater we assume the diffusion distance to be the more we weight the evidence in favor of the conclusion that equilibrium is reached in the glomerulus Furthermore some allowance should be made for a slowing of diffusion by the cell membranes of endothelium and epithelium as compared to water We have purposely chosen a thick diffusion layer of 2 mu

The result of our analysis indicates that the expected difference between inulin and creatinine clearances when filtration equilibrium is 95% achieved is less than 1% considerably less than our experimental error But on the basis of our analysis the discrepancy is still less than 1% even when filtration equilibrium is only 50% achieved The net hydrostatic pressure corresponding to 50% of filtration equilibrium is 60 mm Hg too high to correspond with the facts (22 10) It was chosen high purposely to indicate how inadequate a difference in inulin and creatinine clearances is in distinguishing lack of filtration equilibrum from substantial (95%) equilibrium Our examination of the evidence leads us to conclude that we do not know whether or not filtration equilibrium is reached by the blood in its passage through glomerular capillaries

The next question that we can turn our attention to is a byproduct of this a calculation of the filtration coefficient of the glomerular capillaries The filtration coefficient referred to here is the cubic mm of fluid filtered per minute per square cm of capillary wall per mm of mercury pressure difference across it In Table XII we see summarized the results we obtain The data derived from other authors has required estimating the area of capillaries involved in the experiments reported and is thus subject to considerable error Still I am impressed by the striking difference in the filtration coefficient of renal glomerular capillaries and capillaries in other tissues The differences appear significant We are forced to conclude that glomerular capillaries filter much more rapidly than capillaries elsewhere in the body The experiments of Schwartz and his co workers lend support to this view (21)

TABLE XII

| Degree of Filtration Equilibrium | Net Hydrostatic Pressure at Efferent Arteriole | Difference Between Inulin and Creatinine Clearances | Filtration Coefficient mm /min /cm ²/mm Hg |
|---|---|---|---|
| 95% | 31 6 mm Hg | < 1% | 2 3 |
| 50% | 60 mm Hg | < 1% | 0 28 |
| Source of Data | | Tissue | |
| Landis (16) | | Frog mesentery | 0 049 |
| Derived from Pappenheimer and Soto Rivera (20) | | Dog hind limb | 0 0046 |
| Derived from Landis and Gibbon (17) | | Man forearm | 0 00004 |

*Kety* Could you not have come to the same conclusion a bit more simply? I may be wrong on this but I should venture the opinion that diffusion is somewhat impertinent to the problem of glomerular loop filtration in that these molecules are being translated across the glomerular membrane in a flow of fluid and not diffusing across in accordance with the laws of diffusion In other words to bring up an analogy suppose you are preparing a protein free blood filtrate the sodium ion will appear in that filtrate at the same rate as urea or glucose even though its coefficient of diffusion is greater than those of the larger molecules The fact that creatinine and inulin appear at the same rate in the same concentration ratio across the membrane is because of a translation effect and not a process of diffusion

*Lamport* The method we have employed in constructing our differential equations on the diffusion basis treats the molecules of inulin or creatinine as though they were so widely separated that they are free of interference from water protein and other molecules The analogy is now that of a few stragglers who when they cross the street do so without rubbing elbows none is swept along by others It is possible that the two approaches may actually amount to the same thing The rapid streaming of water across the membrane will give a large diffusion gradient for inulin by constantly washing the low pressure side clean of inulin In this

way, inulin is rapidly transported across the membrane on the diffusion basis

There is another question on the same subject which I should like to interject Can we not regard the non permeating protein as dissolved in inulin as well as in water both of which permeate the capillary wall barrier? Hydrostatic pressure drives both water *and* inulin across the semipermeable membrane in opposition to the osmotic pressure derived from the protein I suspect this is simply a rephrasing of Dr Kety s views It may well be that the crux of the problem is the kind of semipermeable membrane whether it should be regarded as a sieve or in some other manner

*Fremont Smith* Isn t it true that hydrostatic pressure in a filtration system only increases the diffusion and does not change the nature of the process? It is my impression that if you increase the hydrostatic pressure you get more rapid filtration and thereby increase the rate of diffusion You have not altered the nature of the process merely increased its rate

*Kety* I believe there is actually a qualitative difference For example if we have a flaccid bag containing a mixture of helium and carbon dioxide and make an opening in it the helium will come out more rapidly since diffusion is the predominant process operating If the bag is elastic and distended on the other hand or if we squeeze the bag and raise the pressure inside the two gases will come out at the same rate despite their great difference in diffusion coefficients

*Grollman* That assumes that the particles are all the same size It has been demonstrated (cf *J Gen Physiol 9 813 1926*) that ultrafiltration of so simple a solution as sodium chloride for example through a collodion membrane under great pressure may result in a concentration of sodium chloride in the ultrafiltrate which is different from that obtained by diffusion through the same membrane The question arises what type of membrane is the glomerulus?

*Fremont Smith* You are quite right If you want to complicate it your water molecules are not the same because you are dealing with aggregates of water molecules

*Lamport* The filtration coefficient is like the diffusion coefficient. It enters our equations similarly After all osmotic pressure equilibrium is the end result of filtration If you have five

collodion membranes placed serially one after the other but all cut from the same sheet so they have the same permeability, the same osmotic pressure will arise as for one membrane but the time to reach substantial equilibrium say 95% will be much longer with the five membranes than with the one The filtration coefficient depends on time Correspondingly the diffusion co efficient for inulin also depends on time In the differential equation both constants appear only together so that we replace their ratio with a new constant K The units of K are those of pressure

In our other basic equation concerning the diffusion of inulin the rate of filtration of water as a result of osmotic pressure enters and markedly speeds the resulting inulin diffusion rate In other words the inulin equation does not neglect the water it utilizes it That is why I suspect there is little if any difference between the views under consideration

*Wakerlin* Your estimated pressure drop of less than 2 mm of Hg would appear to be in error because for equilibrium of filtration rate to be reached you would have to have a decrease of somewhere around 30 40 mm of Hg

*Lamport* Before replying directly to your criticism let me say I computed the result I reported in two ways I computed it first assuming that the pressure along the glomerular capillaries was everywhere elevated 2 mm above the values for the net hydro static pressure at the efferent arteriole (See Table XII) Then I assumed that intra capillary pressure was not elevated anywhere above the net hydrostatic pressure Both methods yielded the same result indicating that in the range of pressure drop considered its exact size is not critical

Now when I said I assumed achievement of 95 percent of full filtration equilibrium this is how the calculation is per formed We have plasma of 24 mm of mercury osmotic pressure We assume a filtration fraction of 20 percent That means then assuming a linear relation between osmotic pressure and protein concentration that the pressure when complete equilibrium is achieved is 30 mm of mercury (The increase is six mm of Hg out of thirty which is 20 percent) Now if we consider 95 per cent of equilibrium that means the final pressure must be 31 5 mm Hg If we add another 2 mm for the maximum pressure drop in the glomerulus in order again to weight the scales in favor of the

argument we are appraising the efferent arteriolar pressure becomes 33 5 mm of Hg and even then we end up, as I have just indicated with the same result—the argument is found to be inconclusive

EDITOR'S NOTE There then followed a discussion in which the basis for a pressure drop of 2 mm Hg across the glomerulus was disputed No definite conclusions regarding this point could be reached Dr Lamport has since submitted the following Table to summarize his views

In Table XIII I show the values I consider to correspond to 95% and 50% attainment of filtration equilibrium Our analysis does not imply that inulin and creatinine are not good measures of filtration rate They are This type of analysis is not disturbing

TABLE XIII

PRESSURES ASSOCIATED WITH THE GLOMERULUS IN MILLIMETERS Hg

| Degree of Filtration Equilibrium Reached At Efferent End | At Afferent End | | At Efferent End | | Pressure Drop | |
|---|---|---|---|---|---|---|
| | 95% | 50% | 95 | 50 | 95% | 50% |
| Net Hydrostatic Pressure | 33 5 | 62 | 31 5 | 60 | 2 | 2 |
| Osmotic Pressure | 24 | 24 | 30 | 30 | | |
| Net Filtration Pressure | 9 5 | 38 | 1 5 | 30 | | |
| Intracapsular Pressure | 20 | 20 | 20 | 20 | | |
| Intra Capillary Blood Pressure | 53 5 | 82 | 51 5 | 80 | | |

their application in the slightest Apparently what it does disturb is our estimation of the pressure of blood inside of the capillaries in the glomerulus All of the computations used to measure the relationship between afferent and efferent arteriole resistance (10 11 15) and the ones Dr Homer Smith has made (22) are based on the notion that intraglomerular filtration equilibrium is achieved If it is achieved then we know the net hydrostatic pressure of blood leaving the glomerulus is roughly 30 mm Hg and we then have a reference pressure level by which we can compare the upstream and the downstream hindrances

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*Goldblatt* The following session I am sure is going to be different from anything we have had so far and I know that it is going to prove very profitable

Everyone of us has been trying to develop a method to determine the blood pressure of a small animal especially the unanesthetized rat Dr Haas and I have spent much time trying to develop a method which involved the use of the tail (not plethysmographic) but we gave it up because of our inability to obtain consistent results We attributed this to the peculiarities of the caudal artery of the rat I once heard one person in this room

who used the plethysmograph method on the tail of the rat, say that he did not trust anybody but himself My conclusion was that he did not have a good method I hope that we are about to hear about a good reliable simple method for the determination of blood pressure in small animals

Now, as the first contribution on the subject we will listen to Mr Noble and Professor Ballard discuss the capacitance manometer which they have devised

# MEASUREMENT OF INTRA ARTERIAL BLOOD PRESSURE BY MEANS OF CAPACITANCE MANOMETER*

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Figure 13 illustrates the principle of the Capacitance Diaphragm The circular metal diaphragm in its rest position lies in a horizontal plane normal to the plane of the figure and is rigidly clamped at radius $r$ When subjected to pressure from below the diaphragm center is displaced an amount y as shown A plane circular metal electrode of radius Ar is fixed in position parallel to the rest position of the diaphragm at a separation $d$ The electrical capacitance between the diaphragm and the electrode increases with the deflection y The sensitivity of a given diaphragm may be defined as the per unit change in capacitance for a given pressure increment It can be made large by adjusting the separation $d$ so that it only slightly exceeds y at the maximum pressure to be measured

Two fundamental types of diaphragm are the membrane and the plate The restoring force in the membrane is assumed to be furnished by constant tension alone The restoring force in the plate is assumed to be furnished by the rigidity of the material



FIGURE 13

*The Capacitance Diaphragm Manometer provides an instantaneous ink record of blood pressure versus time by the use of direct arterial puncture

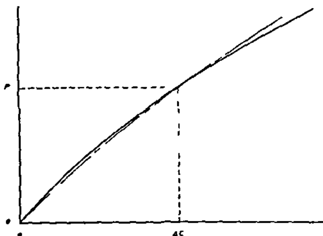


FIGURE 14

alone The actual diaphragm is neither a membrane nor a plate because tension and rigidity each supply part of the restoring force

The solid line of Figure 14 is the actual capacitance increase with pressure The equation of this curve is not known It is probably difficult to determine and more difficult to use in calculations The theoretical capacitance increase with pressure for an equivalent membrane is shown as a broken line fitted so as to coincide with the actual curve at an arbitrarily chosen pressure The equivalent membrane is used in calculations because its deflection curve is a simple parabola and because only geometry and tension enter into the equation The equation for the plate is more difficult and requires knowledge of several physical constants for the diaphragm material

The natural frequency of the capacitance diaphragm is calculated in the following way

(1) The potential energy of the equivalent membrane at deflection y is found by integration
(2) Simple harmonic motion is assumed upon release of pressure
(3) The kinetic energy of the 'effective mass at the rest position is assumed to equal the potential energy at y (i e zero damping is assumed for 1/4 cycle)

(4) The effective mass is calculated to be the mass of the diaphragm and liquid in the diaphragm chamber plus the mass of the liquid contained in the needle reflected back into the chamber

The natural frequency thus found is *210* cps for a size *20* needle *1* inch long This value has not been checked experimentally

The energy required to deflect the equivalent membrane to a given value of y is of interest because it is a source of error and should therefore be small In the case of the diaphragm unit considered this value is 3 39 x 10 inch pounds for 200 mm Hg

The frictional resistance is important since it causes an irreversible conversion of kinetic energy into heat energy thereby distorting the pressure indication The frictional resistance is not known and cannot readily be computed It may best be found by applying a pressure step function to the diaphragm and noting the characteristics of the resulting motion A damped sinusoidal function may be fitted to this curve From this approximation it is possible to calculate the equivalent electric circuit of resistance industance and capacitance for the mechanical system The equivalent electrical circuit is more easily analyzed by electrical engineers Results may be retained in the electrical system or reconverted to the approximate mechanical system

The electrical circuit diagram for the Manometer is shown in Figure 15 The capacitance diaphragm is connected as a part of the frequency determining circuit of an oscillator An additional

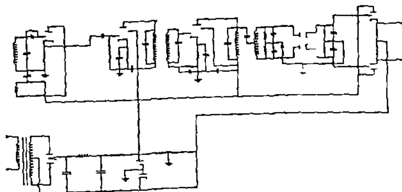


FIGURE 15

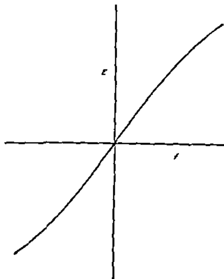



FIGURE 16

capacitor in shunt with the diaphragm unit performs the dual function of adjusting the pressure sensitivity and compensating the circuit for thermal drift As discussed before pressure on the diaphragm unit increases the capacitance and lowers the frequency of the oscillator When the parameters are properly chosen, the lowering of the oscillator frequency varies in direct proportion with the pressure The oscillator output is connected to a standard amplifier limiter and discriminator circuit of a type widely used in Frequency Modulation receivers A cathode follower output stage is employed to permit the use of this instrument with low impedance recorders Pushpull connection is used to balance out variations in supply voltage and to provide zero output voltage at the discriminator null frequency

The discriminator characteristic is shown in Figure 16 The output voltage from the discriminator is zero when the oscillator frequency is adjusted to precisely 10 7 m c Assume that this adjustment is made with zero pressure on the diaphragm Now if pressure is applied to the diaphragm the oscillator frequency will change in direct proportion to the pressure This change in oscillator frequency will result in an output voltage from the discriminator in direct proportion to the change in frequency Therefore

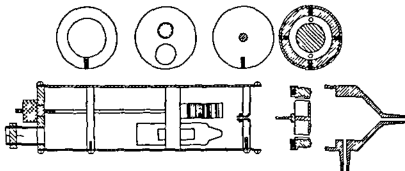


FIGURE 17

the output voltage from the discriminator is directly proportional to the pressure applied to the diaphragm

The output voltage from the discriminator is connected to the input of a Brush D C Amplifier and Ink Writing Recorder

A simplified mechanical drawing of the oscillator unit is shown in Figure 17 The end fitting on the diaphragm chamber carries the needle The side fitting carries a stopcock used to fill the chamber The diaphragm is clamped by means of the threaded ring The fixed electrode is held within this ring by a threaded micarta wafer Adjustment of the spacing between the diaphragm and the electrode is made by twisting this threaded wafer within the ring The diaphragm assembly connects with the body of the oscillator unit by means of a pin jack and set screws so that it may be removed easily for adjustment The oscillator tube and circuit parameters are mounted in additional wafers within a cage like structure formed by threading conductors through holes provided near the circumference of the wafers The zero frequency of 10 7 m c is set by adjusting the threaded rod which projects from the back of the unit This moves a powdered iron core within the inductor of the oscillator thereby varying its inductance and the oscillator frequency Connections between the oscillator and the discriminator are made by a flexible cable which enters the unit through a friction fitting at the back

To place the manometer in operation the oscillator unit is held with the diaphragm end up and the chamber is filled with an anticoagulent solution through the side fitting This procedure prevent bubble formation After a period for warming the oscillator is zeroed to the discriminator null by twisting the tuning

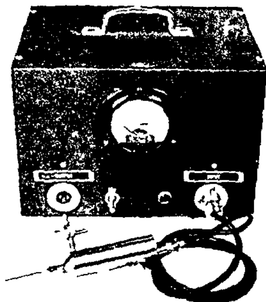


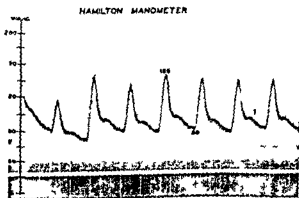
FIGURE 18

slug to center the instrument on the discriminator panel Pressure is applied to the liquid system by means of a mercury manometer and the desired amplitude and position of the pen are adjusted by means of the gain and balance controls on the Brush Amplifier Calibration is marked directly on the record paper Normally only one point is required since the manometer is linear from zero to over 300 mm Hg The pressure scale is continuously variable from a few millimeters full scale to very low sensitivities Three paper speeds are available by use of a simple shift lever These speeds are precise so that a timing signal magnet is not required

In the photograph of Figure 18 the small stainless steel cylinder in the foreground is the oscillator unit The black box contains the discriminator unit and the power supply The instrument on the front panel indicates the discriminator output voltage and is used to adjust the zero pressure frequency of the oscillator The "Output" jack connects with the Brush Recorder

The arrangement for taking pressure calibration is shown in Figure 19 The mercury manometer pressure system connects

Figure 19



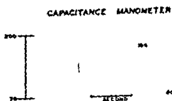




Figure 20

with the diaphragm chamber as shown The chassis on the left houses another discriminator similar to the one in the previous photograph Next is the Brush D C Amplifier followed by the Penmotor

The upper record of Figure 20 was taken from the femoral artery of a man by the Hamilton manometer The lower record was taken from the same patient within a few minutes time by the Capacitance Manometer The average diastolic values compare within 1% but the average systolic pressure obtained by the Capacitance Manometer was of the order of 10% above the Hamilton value This is probably not of great significance because this patient exhibited large variations in systolic pressure between successive beats and the records were not taken simultaneously The time lines of the Brush penmotor are curved because the pen moves in an arc transverse to the paper motion

In order to obtain a record having straight time lines it is necessary to move the Brush record to the left by an amount depending upon the distance of the portion of the record from the center of the chart paper An approximate correction is shown by the light lines in Figure 21 The angle of deflection of the pen is proportional to the input voltage Therefore the amplitude of the pressure wave cannot be measured along a line perpendicular to the direction of motion of the paper but must be measured along the arc in which the pen moves The maximum error from this cause is no larger than 0 8% and will usually be far less The greatest accuracy for comparison with straight time line records will obtain when pressure calibration is made very near the systolic and diastolic values respectively when the record amplitude is fairly small and when the record is centered on the paper

The comparison between the Hamilton Manometer and the Capacitance Manometer traces is seen to be considerably better when the time-line correction is made The blunt peaks on the lower trace may be due to the fact that the Brush Penmotor is *flat to 100 cycles/second only whereas the frequency response of* the Hamilton instrument is higher

Figure 22 is a record of a hypertensive dog taken with the Capacitance Manometer Three paper speeds of 5 25 and 125 mm /sec are shown



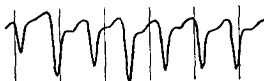


FIGURE 21

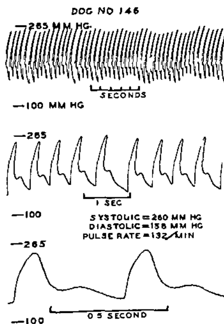



FIGURE 22

*Lamport* Have you tested the fidelity of the Brush instrument yourself?

*Noble* Yes I used a Hewlett Packard Audio Oscillator to check the frequency response When the penmotor is used with the Brush D C Amplifier the frequency response is very flat to about 95 cycles per second where it drops off rapidly When the penmotor is used alone it exhibits a marked resonance at about 30 cycles per second and a rapid decrease in response with increasing frequency above this point The D C Amplifier contains a compensating network which serves to flatten the frequency response of the recorder

*Bazett* Does the capacity of the cable bother you at all?

*Noble* No We had to go to special pains to take care of that The oscillator circuit is unusual in that output is taken from the cathode circuit so that the output impedance is low of the order of 50 ohms Capacitance variations in the cable are not of appreciable importance because the output impedance is low and because the capacitance measuring circuit is effectively isolated from the cable

*Bazett* It is a pity that the authors report the meeting of many difficulties which we have been through The description of later modifications of Lilly s manometer has been in manuscript awaiting publication for about a year and one half It has just been out about a week We have records on hospital patients for something like three thousand hours None of this has been available except for a brief report just published in the American Heart Journal

*Schroeder* How does this manometer differ from the Lilly manometer?

*Noble* I do not know what circuit the Lilly manometer employs The capacitance pick up unit is similar

*Bazett* In the recent publication is the diagram of the penultimate of the present Lilly circuit The capacitance manometer appears to be the best solution at the present time I doubt whether any one type of instrument is superior to any other Different problems require different instruments The Lilly manometer in its present form with a 20 gauge needle would follow about 800

vibrations a second Its real value depends upon its low volume displacement For the rat that may be an important consideration Do you know what the volume displacement is per 100 mm in your instrument?

*Noble* I have not figured that I have expressed this information as energy required to deflect this instrument to the 200 mm position

*Bazett* The original capacity manometer built by Lilly in my laboratory in 1940 had a displacement of less than a millionth of a cc per 100 mm of pressure The Sanborn instrument has a displacement some 20 times larger When Lilly gave his second description he tried to express the relationship of the charac teristics of the manometer to its volume displacement Unfortu nately he used a very sensitive membrane on which to base the argument This membrane has been assumed wrongly to be the standard Although this special membrane is more sensitive it has a twenty times larger volume displacement

*Noble* There is another consideration too and that is what you are going to use for a recorder

*Bazett* We are using the Brush Instrument

*Noble* If you are going to use the Brush direct writing oscil lograph there is no point in having a very high frequency response in the pickup head because the Brush Recorder will follow vari ations to 100 cycles per second only Therefore a natural fre quency above 200 cycles per second is of no use

*Bazett* It seems to me that the important feature is the vol ume displacement rather than the frequency If the volume dis placement is small enough you can then use small connecting tub ing In the Lilly we use a 26 gauge needle In order to attain maximal convenience we use a plastic tube connection which has an inside diameter of 0 25 mm This can be done only with instru ments which do not require a larger motion because there would be frictional loss

The stretch of the wall of any tube is the function of the internal pressure and radius The smaller the radius the less the risk of stretching If you want to use a plastic tube you must go down to the minimal possible size you can handle and yet you must avoid frictional losses We are using the small displacement

not for the frequency, but for the fact that it allows us to utilize very small tubes

*Noble* In ordinary arterial puncture recording concerning which I was speaking at least 95 percent of the effective mass of the diaphragm is contributed by the needle If a small tube of considerable length is used instead of a needle the effect is greatly to increase the effective mass and resistance of the hydraulic system and possibly also to decrease the elastance Under these conditions it is necessary to increase the elastance of the diaphragm to as large a value as possible in order to obtain an acceptable frequency response This may be accomplished by making the displacement small The use of small tubes was not planned for this instrument

*Ogden* There is another point in connection with going after very high frequency Even in the relatively slow long cardiac cycle of the dog I am not convinced that anybody knows what are the frequencies of the most rapid components of the beginning of systole Hence we do not know what the precise systolic pressure is

*Lazett* We have records made with a Lilly manometer connected to a General Electric oscillograph and to a Brush ink writer at the same time

*Ogden* I wonder whether D C amplifiers follow the high frequency component at the beginning of systole

*Noble* The D C recorder does not distort the frequencies of the order in which we are interested

*Schroeder* Is the output of your manometer itself high enough to use a Heiland galvanometer? This problem might be studied The Heiland galvanometer is of very high frequency

*West* A Heiland type G galvanometer deflects 2 07 radians per milliampere

*Noble* This manometer may be used with many types of galvanometers by making minor modifications to the output circuit

*Katz* With equipment such as the Lilly the Warburg the Sanborn and the inductance manometer we seem to be advancing in the development of electrical manometers In 1911 an engineer Frommer worked out a capacitance manometer with a coaxial

cable in my laboratory (Frommer J C *Electronics, July 1943*) A special device in our instrument made it possible to eliminate completely the capacitance effect of the cable What we need is for the Bureau of Standards which has highly specialized skills along these lines to help us outline specifications for these various pieces of apparatus and tell us when we should and should not use each of them In other words for those of us who cannot talk in engineering terms I would like to have this thing put in non technical terms so I could understand it and arrive at my own judgments

*Lamport* As I recall it Dr Wiggers concluded that 100 cycles was the highest harmonic that was found in the pulse pressure wave I do not know how high his own recording system went I do not know whether he could have gotten still higher harmonics if his system had gone higher But that was the conclusion he reached Ordinarily I believe if you are trying to get complete fidelity with all harmonics present you try to use an instrument which is faithful to at least four times that frequency which would give you four hundred

I spoke to Rappaport who did the work with the condenser manometer at Boston

His criticism of increasing the sensitivity in the manner fol lowed by Lilly is that there is very little benefit because of the fact that the elasticity of water itself becomes a limiting factor If you stiffen your membrane progressively to reduce the volume dis placement for a given pressure change the elasticity of water itself becomes so important a part of the elasticity of the whole system that you run into the region of diminishing returns where further stiffening of the diaphragm is inconsequential

As far as the condenser manometer goes I consider it expen sive but useful However in the future I believe our manometer of choice will not be the condenser I expect the reluctance manom eter to be the future tool for pressure measurement in physiology

The reason is twofold I think it will give you much more output and as a result require less amplification and that it is simpler than the other types The reluctance manometer is based on the principle that moving a small piece of iron inside a coil changes its inductance markedly Iron has a magnetic permeability of several thousand and the permeability of air is about 1 so if

you move something with a permeability of several thousand you can make a tremendous change in the reluctance of the magnetic circuit and so in the inductance of the coil With a condenser you do not have such an advantage If you move a condenser plate 10 percent of the distance to the other plate you have changed the capacitance by only 10 percent That means you have really got to step your output up As soon as you get into considerable amplification of low level signals you have to have carefully designed expensive instruments and everything else that they imply

The reluctance manometer is now designed so you can have inherent compensation The strain gauge manometer suffers from hysteresis you cannot reproduce your zero setting satisfactorily and you do not get exactly the same calibration from one time to another The reluctance manometer as far as I know has in this country only been worked on first at Wright Field and then at the Mayo Clinic and is still in a relatively early stage Its promise is great It was first described by Wetterer in Germany and brought over by a student of his who had worked with it in his laboratory (6 25) * Its output is very high compared with the other instruments which people are using and its size is wonderfully small You can attach it to the end of a cardiac catheter I believe a good deal of the fluid transmission problems which the designers of condenser manometers are wrestling with can be solved by placing the manometer inside the blood so that fluid pressure transmission is replaced by electrical transmission

*Katz* The whipping effect of a catheter with a heavy mass at the end may give greater distortion than when the capacitance is not at the end If you put capacitance in the catheter it is the same problem which you are trying to avoid I think you can compensate for the overshoot of the ordinary catheter by electrical damping

*Cournand* With regard to a pickup at the end of a catheter there are still according to Gauer with whom I talked a few days ago a number of problems to solve in the matter of amplification A few years ago we used an electrical system based on reluctance and compared the curves which were obtained simultaneously with the Hamilton manometer There was a two stage amplification With regard to the capacitance condenser is Mr Noble familiar with the physical characteristics of the manometer developed

* See Page 131

by Warburg and Hansen and with the superb tracings obtained with it?

*Bazett* We obtained two of Warburg's manometers They give satisfactory deflections only if a large needle is inserted in the vessel The Warburg is not linear and it is also inconvenient to use

*Dexter* What is the volume displacement on the Warburg?

*Bazett* About the same as the Sanborn manometer The trouble with the Warburg instrument is that it has too large a diaphragm Therefore the compressibility of water sets a limit here We have used small diaphragms which however are not free from other troubles

*Cournand* May I add that if you go into the problems of hemodynamics in hypertensives you will be anxious to have as good tracings as possible I have worried about this problem That is why the engineers should know exactly what our worries are

*Shorr* We set certain specifications in our original request to Mr Noble and Professor Ballard which they have met admirably We now can set other specifications

*Goldblatt* Our main purpose on this occasion is the presentation of methods for the determination of blood pressure in small animals particularly the rat I thought that it would be a good thing for all of those who have had experience with the determination of blood pressure in the small animal by any means whatsoever to tell us about their method and experience

Will Professor Ballard add to what Mr Noble has said and also tell us whether there is any possibility of applying their type of instrument to small animals

*Ballard* It must be realized that there are two contrarily operating factors One is the question of reliability and the other is the question of sensitivity There is relatively very little difficulty in making the present equipment which Mr Noble described many times more sensitive In the first place its sensitivity is enhanced to a tremendous degree by the particular circuit which is being used The capacitance of the diaphragm against which the pressure was measured varies by a very very small percentage This capacitance tunes the oscillator This oscillator oscillates

at 10 000 000 double vibrations per second The total variation in frequency when measuring the maximum pressure involved is only a few thousand cycles We are shifting that frequency by a very very small fraction of a hundredth of a percent It is quite possible by using a more sensitive discriminator to make this equipment more sensitive and by the way I don t know whether Mr Noble made it clear to you that what he has used here is essentially the fundamental basis of the so called FM radio broadcasting system the frequency modulation broadcasting system and his little box which he showed you with the meter is essentially an FM receiver The FM transmitter station is the tube which has its frequency shifted its frequency modulated by the change of the capacitance of the diaphragm itself Now it would be a fairly simple matter to make the meter give a full scale deflection say for one quarter the frequency deviation for which it does it at the present time and that would mean then that there would be one quarter of the voltage required to produce that pressure indication and the question of frequency range etc would be improved But, on the other hand it is a question of additional reliability a little greater difficulty in adjustment perhaps and in keeping it in adjustment and as a matter of fact what we tried to do is to hit a happy medium between those two conditions making it not too hard to adjust and at the same time give adequate sensitivity for the work it is supposed to do

I would like to call your attention to one point the capacitance manometer record showed a very sharp break at the bottom The lower part of the wave came down rapidly and then there was a rather sharp peak there Theoretically if that is a point an absolutely sharp point it is an indication that the particular instrument would have to be sensitive up to infinite frequency In other words the sharper the point the wider the frequency band required to produce it I wanted to call your attention to the fact that with a sharp point in a record of that sort it indicates the instrument is sensitive up to quite a wide upper range of frequency There is no difficulty in producing a record that is as perfect as the operation of the diaphragm

We as electrical engineers are surprised that the cathode ray oscillograph is not more often used for your recording work The cathode ray oscillograph can be obtained with a long persistence screen and compared to medical instruments by and large

it is not too expensive It can be made to give you an exact replica of what is coming out of the manometer head

I confidently predict that before many years there will be many more cathode ray oscilloscopes around in your laboratories where you are interested in manometers of this type

*Dexter* Is it possible to get a permanent record Professor Ballard?

*Ballard* The oscilloscope can be photographed

*Pitts* You mentioned the effects of temperature When you speak of an instrument of this size you always want to keep the thermal drift in mind

*Noble* I was forced to reduce the sensitivity of this instrument in order to compensate for frequency change with temperature

The capacitance diaphragm is connected in shunt with a fixed padding capacitor The temperature coefficient of capacitance for this padder is chosen such as to correct for changes in the oscillator circuit parameters with temperature

*Katz* The strain gauge is not as commonly used as it might be I understand that some of these may be used directly at the receiving end of the catheter

*Noble* That system has been used To my knowledge at the present time manometers which use strain gauges are very much slower than either the capacitance or reluctance system

*Cournand* What is the sensitivity of the membrane in terms of deflection Mr Noble?

*Noble* The approximate deflection at the center of the diaphragm is two thousandths of an inch when subjected to 200 mm pressure

*Cournand* When we speak of sensitivity we are interested in the deflection on the tracing to be recorded What I am asking in other words is the deflection in millimeters in terms of millimeters of mercury of pressure as recorded?

*Noble* The deflection sensitivity is continuously variable from very great sensitivity to very small sensitivity depending upon the gain setting of the amplifier which is used for recording

*Cournand* What are the limits that you set for yourself?

*Noble* Those limits are determined by the type of recorder that you wish to use I can give you the output voltage of the discriminator in terms of the pressure The output voltage is of the order of 10 volts for 200 mm of pressure on the manometer The actual pressure scale that you obtain will depend upon the gain of the amplifier which you use for recording You can have full deflection of the order of 2 or 3 mm or have full scale deflection at several pounds per square inch depending upon the setting of the gain of the amplifier

*Lamport* Do you get good stability on your paper with full deflection on 2 mm ? In other words is that usable?

*Noble* Not with the capacitance unit that we use in this particular instrument because this capacitance unit was designed to be used with dogs with pressure of the order of 100 200 mm of mercury or better You can by using thinner capacitor diaphragms increase your sensitivity so that the stability is very good with a few millimeters of pressure

*Katz* Dr Dexter tried the Sanborn manometer I wonder whether he would want to comment on his practical experience

*Dexter* One useful point for those of you who are using this manometer is this In order to have a stable instrument it is necessary to warm the amplifier for a matter of several hours We usually begin our experiments about 7 30 in the morning We have a time clock which turns on the amplifying unit automatically at about 4 00 A M This has eliminated practically all of our difficulties

The Sanborn Company also have another transducer unit by which a full scale deflection is obtained with one or two mm of water pressure In this range of very high sensitivity the instrument is less stable than in the higher ranges of pressure

*Goldblatt* Gentlemen this may be a good place to call on Dr Anderson to tell us about her blood pressure methods

*Anderson* This simple device for measuring blood pressure in the unanesthetized rat has been described by Farrell and Anderson (Farrell G I and Anderson F *Proc Soc Exp Biol & Med* 72 461, 1949) It consists in placing a cuff permanently around the

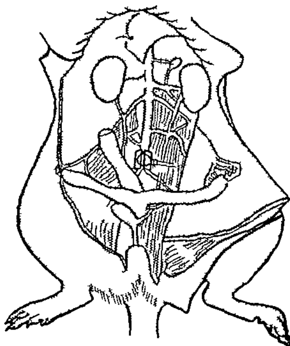


FIGURE 23 Plastic cuff placed around abdominal aorta

abdominal aorta and measuring the pressure in the aorta indirectly by means of an oscillometer and mercury manometer

The cuff consists of a shell of plastic tubing 6 mm in length and 4 mm inner diameter into which is fitted a latex bulb 4 mm in diameter A piece of polyethylene tubing is fitted into the bulb so that it can be inflated The cuff is placed around both abdominal aorta and vena cava just above their bifurcations The vena cava is included because it simplifies the operation if the two vessels are not dissected free of each other The blood pressure readings appear to be the same whether or not the vena cava is included in the cuff Figure 23 shows the cuff in situ The cuff is fastened securely to the body wall and the tubing from the bulb is brought through the posterior abdominal wall and carried under the skin to the back of the neck where it is brought to the outside

Blood pressure readings are made with the use of an improvised oscillometer and a mercury manometer The apparatus is

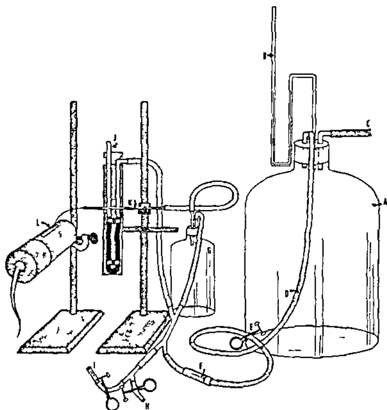


FIGURE 24 Oscillometer connected to the animal

shown in Figure 24 The animal holder (L) shown in the figure has been replaced by a 1000 ml beaker with a perforated cover When the rat is placed in the beaker there is no struggling since the animal is not uncomfortable or irritated in any way The tube from the cuff is connected with the capillary tubing (K) which is connected with the pressure bottle (G) A drop of colored alcohol in the capillary tube shows the oscillations transmitted from the aorta as the bulb of the cuff is inflated As the pressure is raised in the cuff and oscillometer the alcohol bead travels toward the cuff and shows distinct oscillations which gradually increase in amplitude and then abruptly diminish A reading is made on the mercury manometer at the point where the oscillations abruptly diminish

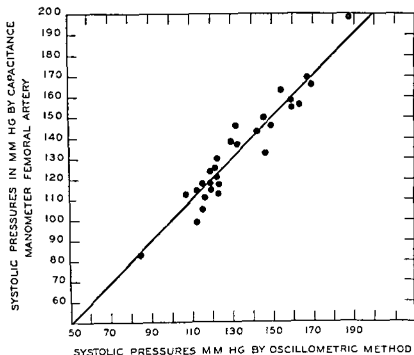



FIGURE 25 Graph showing the relationship between the intra arterial pressure in the femoral artery and the pressure in the aorta by the oscillometric method

The readings obtained on the pressure in the abdominal aorta by this indirect method have been compared with the systolic pressure in the femoral artery measured intra arterially by means of the capacitance manometer which Mr Noble has just described These readings were made on rats anesthetized by ether Immediately after the intra arterial reading while the animal was still under ether the blood pressure reading on the aorta by the cuff method was taken The comparative data are shown on a graph in Figure 25 The intra arterial systolic pressure for a given rat is plotted as the ordinate and the pressure reading by the cuff method as the abscissa The diagonal line represents perfect agreement The readings by the two methods tend to fall along this line The average intra arterial systolic pressure on 19 normal adult rats under ether was 121±15 mm Hg by the cuff method on the same rats taken immediately following the intra arterial reading the average was 118±15 mm Hg The average of 540 blood pres

sure readings by the cuff method on 20 normal adult rats un anesthetized taken over a two month period was 130 mm Hg

*Dexter* Would you consider this to be systolic pressure?

*Anderson* I should like Dr Ogden to discuss that

*Ogden* I spent a short time in Dr Anderson s laboratory Records were taken from the femoral artery of anesthetized rats with the capacitance manometer which Mr Noble has described The systolic pressure as determined by Dr Anderson s method coincides fairly closely with the systolic pressure as recorded by the capacitance manometer The term systolic should perhaps be modified since using a Brush ink recorder on a rat with a very rapid heart rate we cannot be certain what is the basic frequency of the initial component viz the initial systolic surge With Dr Anderson s method the systolic pressure is read at the point where the pulse oscillations disappear At this same point the capacitance manometer continues to record at the same pulse pressure for a significant period As the cuff pressure is increased further the capacitance manometer record shows a diminution of pulse pressure and then an almost complete occlusion It would appear that the cuff method although not recording the systolic peak at least indicates the effective systolic pressure

*Lamport* Do you get the same pressure if you occlude the vessel completely and let the air out as done in human measurements instead of working on the way up until the first point of oscillation?

*Ogden* Dr Farrell tried that and got very nearly the same results only a two or three mm difference consistently He felt that he was doing better on the up scale than on the down scale

*Cournand* The systolic pressure in the femoral artery is higher than in the aorta

*Schroeder* May I suggest that this may represent the breaker phenomenon which was discussed earlier and which Bradley and Wilkins reported Dr Bazett might describe the experiments he did on isolated strips of arteries The principle states that when a wave is moving up a short its crest travels faster than its trough It is tipped so to speak the systolic part of the wave becoming steeper and the crest higher This can be easily shown in experiments on man The diastolic elevation which one gets beyond the

cuff or beach is probably due to lack of regurgitant flow which causes more blood to run off through the periphery

*Ogden* That may well be if the cuff is elevated to or above the systolic pressure Why is there any through flow in the forward direction if it is to or above it? Why is it a measure of the systolic pressure?

*Katz* I would like to comment In blood pressure measurement the width of the cuff is an important item You may not have sufficient width For the rat you may have to work with a width of the balloon based on the size used in man

*Lazett* We reported (*Amer J Physiol* 112 *182 1935*) an experiment which may have a bearing on your work The femoral artery was cut in two places and a T shaped cannula inserted in each place Each of these was connected to a Wigger s manometer In between the manometers was placed a piece of carotid from another dog which passed through a glass tube The tube acted as the compressor of a Riva Rocci sphygmo manometer The pressure through these arterial segments was about 140/90 When the arterial segment was compressed the pressure above it rose to about 150 160/90 because of wave reflection and development of end pressure As soon as air pressure falls below the end pressure the pulse passes through

Dr Anderson recorded a higher pressure than the lateral pressure in the aorta so that it checks fairly well with these experiments You actually might record a pressure a little too low if the latex cuff had a certain amount of tension taken up on the wall which should be subtracted from your reading

*Goldblatt* We are mainly interested at this moment in a discussion of methods that could be used frequently on the same rat preferably unanesthetized

*Ogden* I think this method is one such possibility

*Bazett* What are the diameters of the femoral the carotid or the aorta of the rat?

*Anderson* An 18 gauge fits into the carotid of the rat The rats we use weigh about 250 gram In the femoral we use a 22 gauge needle

*Lazett* Do you insert your needles into the arteries and the carotid through the skin?

*Anderson* We anesthetize the rat when we puncture the carotid or femoral arteries

*Lamport* In your indirect method you have air transmitting the pressure in the system If you are to get pulsation of the alcohol globule there must be a change in pressure in a fairly large air system If you have just a small compression of the detecting bulb it might not be adequately transmitted by the large volume of air Instead of using air you might use water

*Anderson* The difficulty is that one gets air bubbles in water

*Lamport* Could you use oil or gasoline in your transmission system?

*Anderson* If you could make it tight and not have some of the fluid leak out and air bubbles get in We tried putting in saline and leaving it but it was not practical

*Ogden* I believe this indirect method should be compared with the other indirect methods on the rat rather than being compared with the direct methods which are designed for other purposes The only reason for applying the direct method to the rats in which this was being tested was to determine the accuracy of the method

*Schroeder* I would like to suggest for your consideration the photoelectric plethysmographic method for the rat We have used it on over two or three hundred rats and have found it to be most satisfactory This is the method developed at the Lederle Laboratories A light is passed through the hind foot onto a photo cell which is connected with a simple circuit One reads a microammeter and an anaeroid manometer A cuff is placed about the rat's leg and inflated When it is deflated to systolic pressure the galvanometer needle deflects Measurements can be repeated a number of times and the readings are reasonably consistent It has the advantage of not disturbing the rat especially when he has been trained It is not necessary to warm the animal We have used the Sobin method but found it laborious and slow Because of the rapidity and simplicity of this new method we are using it exclusively The only disadvantage is that the procedure must be carried out under a red light so as not to affect the photo-cell

*Goldblatt* Is it entirely objective?

*Schroeder* The pressure is read when the galvanometer deflects as the leg fills with the first systolic impulse

*Goldblatt* You get only systolic readings?

*Schroeder* You get only systolic readings as with almost all indirect methods

*Ogden* Would this be more objective than a deflection of a meniscus?

*Schroeder* The deflection is sudden and very pronounced

*Dole* Would you describe the occlusive cuff a little more in detail? In my experience these cuffs are difficult to apply since if too tight they produce congestion and if too loose they fail to transmit the full pressure to the leg because of the opposing elastic force of the bag itself

*Schroeder* The cuff is inside a small cloth bag which is wrapped around the leg Gauze is then used to apply the cuff tightly to the rat s leg Readings are quite constant averaging 110 130 mm systolic pressure

*Dexter* Did you check this with the Hamilton manometer or other similar instrument?

*Schroeder* Yes we have compared it with Hamilton records in anesthetized rats

*Goldblatt* I saw the original Subero instrument in operation The range of oscillation was so great that I found it difficult to decide on the end point I know that Dr Walter Heymann at Western Peserve University is using the method and that he is well satisfied with it

*Schroeder* We are satisfied with it and we prefer it to any other indirect method With trained rats we can do ten or more animals an hour When they are untrained a determination is difficult

*Grimson* I would like to discuss a tail plethysmograph method We started out with the Sobin method studying two things effect of stilbestrol (diethyl stilbestrol) and production of neurogenic hypertension in rats That was about four years ago We

came to a bad end with the neurogenic hypertension and blamed it on the apparatus This was apparently right at that time We spent about a year and one half working with transillumination of the tail with all sorts of gadgets until Leonard and Skeggs came along with their carbon button That was along the same lines as our work and we got one However we had some difficulty in determining the end point Mr Hill one of the men in the laboratory, developed the idea of putting an amplifier circuit on it With the circuit and a head phone set instead of watching an ammeter and a water manometer simultaneously we simply reduce the cuff pressure and watch the mercury manometer until the telephone rings in our ear The change in pitch at the end point is very clear It is a convenient end point which is recognized instantaneously Whether we are recording systolic pressure I don t know

We compared this procedure with the Leonard and Skeggs method with the original Grollman plethysmographic and water manometer method and under anesthesia and with the direct cannula method The last was difficult since we cannot cannulate the aorta and still get a tail reading We therefore used the carotid Generally there has been a little step up of pressures using the ear phone method Our readings averaged about three to five mm Hg higher than they did when we were using the plethysmograph under the circumstances in which it could be used at that time We were then following the suggested methods and heating the rat for 10 minutes However with Priscoline and without heat readings were obtainable for a period of eight or ten hours As time went on these two methods of dilating vessels in the tail were discarded and we joined alternately two great conflicting schools of thought First agreeing with Dr Handler and his group we conformed to the belief in heating the tail If you heat the tail sufficiently you can heat the rat Handler avoids that by heating the tail only for short periods All of his equipment is in a heat box with the tail The rat is outside This works reasonably well Later we joined the other school of thought held by some of Dr Kempner s group studying diet in the rat According to this belief we leave the rat not at a heated temperature but in a constant temperature box kept at or just below the temperature of its body In other words the rat is warmed a temperature of 31 to 37° C for half an hour at the end of which time the end point can be read

Our whole feeling has been that although rat tail blood pressures are not the most satisfactory thing in the world there are nevertheless experiments to be done The carbon button head set and body warming method seems the simplest way in which we can get some sort of a reading in experiments involving many pressures on many rats We are not worried as to which method heating tail or warming rat is the best Neither group preferring one method will deny that you can go in to use the other man s equipment and get a reading Also you can have three or four or six technicians take consecutive readings which agree remarkably well

*Schroeder* Is your method similar to that of Friedman?

*Wakerlin* We heat the tail at 40 degrees Centigrade for fifteen minutes We think the plethysmograph method is reliable and have been using it for about a year and one half We find that depending upon the rat we get readings which are anywhere from 80 to 120 mm Hg representing the systolic pressure in the arteries of the tail For any one rat it varies from one time to another At one time it is 100 and then it is 120 at another The rat is in a lucite container which is an advantage because the rat is under constant observation Furthermore the rat after struggling the first time or two finds it cannot get hold on the lucite container and gives up and is quiet We feel the method is reliable and we get very definite rises in blood pressure when we operate upon the kidney to produce hypertension

*Schroeder* How many determinations can you do in a day?

*Wakerlin* I should say at the rate of four or five per hour

*Grimson* We use the technique of maintaining animals in a long heating box in which 8 to 12 cages can be placed Each time that a cage is removed you can replace it by one at the other end of the box You can thus have a continuous line with each rat having been maintained at body temperature for half an hour I think numbers are essential with methods as good as this and you must run from 10 to 20 per hour

*Wakerlin* We found it important to have the temperature of the tail constant If the thermostatic arrangement is defective and the temperature goes over 40°C the rat is uncomfortable and the pressure reading is not reliable

*Ogden* We have been using essentially Dr Grimson s procedure The rats are placed for about fifteen minutes in a box at

about 37°C and then transferred to room temperature and into a thermostatically controlled tail temperature cuff. We use a glass holder instead of a plastic one. Under those circumstances the reproducibility of consecutive measurements taken one after another is extremely good. Day to day variations of 10 to 15 mm Hg are encountered.

*Schroeder*: Has anyone had experience with Friedman's method?

*Ogden*: He uses a microphone and a particular type of amplifier between the microphone and head phones. The apparatus has special electrical characteristics which tend to emphasize those frequencies which are characteristic of the systolic sound and to de-emphasize those frequency characteristics of adventitious sounds produced by tail movements.

*Grimson*: That is important. However, although one can say that a characteristic change in the audible sound occurs at about systolic pressure, I doubt whether any claim is made that the change occurs precisely at the systolic pressure.

*Dole*: I would like to comment on the rat tail method. We set up the Sobin apparatus modified by the substitution of a glass plethysmograph for the original metal one.

Our original concern in setting up the method was to satisfy ourselves that we could obtain consistent readings after an animal had been in the instrument for some definite time. In this we were disappointed since readings taken at about two minute intervals during the first half hour failed to become steady at any value. In the attempt to find a steady state we extended the observations for periods up to five hours in a few experiments, readings being taken at about five minute intervals. Variation of readings continued.

Some of the variation in the prolonged experiments seemed to be related to changes in room temperature. We therefore put the entire assembly in a large incubator so that the environmental temperature could be controlled. We were not able to obtain consistent readings within an observation period of an hour at air temperatures of 20, 25, 30, or 35 degrees Centigrade and with the plethysmograph water jacket temperature at either 40 or 42 degrees.

In other experiments with this arrangement we changed the

environmental temperature between 25 and 35 degrees in a step wise fashion during a long period of observation The apparent blood pressure as read from the instrument tended to follow these temperature changes In one experiment the readings were caused to vary up and down with the temperature through three cycles the readings changed from about 95 to about 160 mm Hg as the incubator temperature changed from 27 to 35 degrees This seems to indicate that there is an environmental temperature effect on the apparent blood pressure

*Grimson* We have been carefully following the rectal temper ature We feel it is important not to disturb and to maintain it as constant or normal as possible minimizing perhaps physiological reflexes many of which would occur during actual heating of the whole animal

*Grollman* You always get abnormally high readings if you overheat the rat That may be shown by taking successive readings on an animal left in the heater continuously It does not take very much overheating to give them fever and then of course you get abnormally high readings There is a plateau before their body temperature actually rises during which time you can obtain con stant results

*Dole* That was our hope We did not however observe a plateau at any environmental temperature

*Grimson* You don t know the rat s temperature just the temperature of the environment Heating the tail will heat the rat variably depending upon the time of heating the tail so there is a shifting factor there that was not controlled unless you knew the rat s temperature

*Dole* We did not measure the rats temperatures All that we observed was a change in the apparent blood pressure associ ated with change of environmental temperature

*Schroeder* Dr Seymour Reichlin now at New York Hospital spent a long time as a student studying the adrenal cortex of rats He found some bizarre results Merely taking the animals from the rat room to the laboratory where they were killed caused dis charge of the adrenal cortex to about half the maximal response as measured by the fall of ascorbic acid Therefore the controls had to be controlled Summer St Louis weather caused a doubling of the weight of the adrenal When he worked in the rat room

quickly and controlled the environment reproducible results were obtained

*Zweifach* It is important also to carry out your blood pressure procedures in a room that is free from extraneous noises

*Dole* I think we would agree with you on that

*Zweifach* I cannot see the advisability of keeping the rat imprisoned in the blood pressure apparatus for extended periods of time and then to expect that the blood pressure would not change Such a procedure does not constitute a test for the reliability of this instrument It simply indicates that prolonged exposure in the apparatus is undesirable We have found that it is necessary only to keep the rat tail in the warmed holder for 5-10 minutes in order to obtain a satisfactory reading A more satisfactory approach would be repeated observations over a period of days—or two to three times daily—for several days leaving the rats in the apparatus for as short a period as possible each time

*Dole* Our problem is simply that we have so far not been able to obtain a consistent base line This difficulty is illustrated by an experiment done in a quiet room with an animal who had been accustomed to the procedure by daily measurements during the preceding week The environmental temperature was 33° C and the plethysmograph jacket temperature was 10° C During a three hour observation period we did not find a plateau in the readings

*Zweifach* This is probably the result of restraining the rat for so long a period of time

*Grollman* You excite them and make them restless by keeping them that way

*Dexter* I think Dr Dole has an interesting way of checking on the method I am not at all convinced that the rat is any more uncomfortable at the end of an hour than he was at the end of 10 minutes

*Grollman* The rat cannot possibly be comfortable if incarcerated and under restraint as it must be when placed in this type of apparatus If you want to restrain the animal properly, anesthetize it and measure the pressure by the indirect method and compare this reading with that obtained directly from a cannula placed in the aorta and connected with a mercury manometer A ther

mometer placed in the rectum will indicate whether or not the rat is being overheated

*Grimson* I might comment on certain control checks which should be made One of them is to note whether heating the tail is heating the rat If tail heating is to be done you must avoid long exposures so as not to heat the rat If you do abnormal disturbances will develop We all agree

Secondly the rat should be in an environment to which it is acclimated preferably in the same room with the pressure apparatus There are some objections to this but at least the conditions should be kept constant Even when exercising precautions not to raise the body temperature by excessive warming of the whole rat or the tail there will be variations

When one records blood pressure repeatedly in dogs readings may vary from day to day as much as from 160 to 120 particularly in normally active alert animals In rats why is there such a controversy? The problem is similar I would like to present what seems to be the next logical step in chronic blood pressure experiments in unanesthetized animals

*Katz* I would like to reiterate what Dr Goldblatt said It appears that the measurement of the blood pressure of the rat is a personal method and unfortunately not for general use I had several technicians working with me on a colony of rats for a whole year but could not use their data I am still not convinced that any of the indirect methods are objective

*Grimson* Here is a way to get around the variability which is encountered admitting certain variations which occur at random no matter what the experiment is The type of the experiment does not matter The point I want to illustrate is that although experimental results differ individually day by day pressure readings are fairly uniform This is accomplished by having each dot on the graph represent the average of blood pressure readings taken on ten rats This minimizes the possibility of variation occurring were we to get in one instance a single reading of 160 mm Hg We know that rats don t have normal variations as high as 160 With this method of averaging and making numerous readings we perhaps have removed inconsistency by increasing the number of experiments I don t think these results can be thrown out entirely in the absence of another method for carrying out such measurements

# THE DIFFERENTIAL IMPEDANCE RECORDER FOR BLOOD PRESSURE MEASUREMENT BY INDIRECT MEANS

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*Cornell University College of Engineering*

The Differential Impedance Recorder originally devised by DuBois and Sims of Yale has been modified in an attempt to obtain the systolic blood pressure of rats by indirect means

This instrument is a phase-sensitive radio-frequency bridge for measuring the electrical impedance between two points on the skin surface of the rear foot The impedance between points A and B Figure 26 varies in a periodic manner with the phase of the heart cycle as long as there is no restriction of the blood supply to the limb If a pneumatic cuff is interposed between the heart and the electrodes A and B and the pressure within this cuff is raised above the systolic value the circulation is shut off at the cuff and the impedance between the electrodes ceases to vary with the heart beat As the pressure within the cuff is lowered eventually a point is reached where variations in impedance at the heart rate are first observed The pressure in the cuff at this point is systolic blood pressure approximately

This method is accurate and not very difficult for the measurement of systolic pressure in anesthetized rats When used with unanesthetized animals the instrument is difficult to use because random leg motions produce contact resistance changes and body



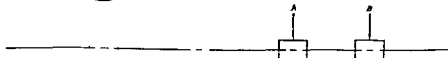





FIGURE 26

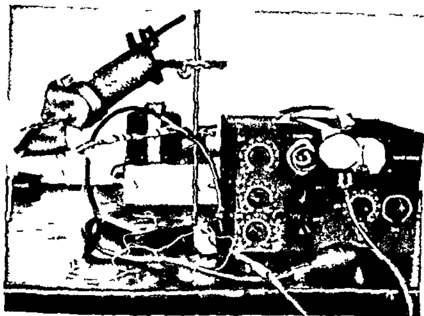


FIGURE 27

capacitance signals which are many times the order of magnitude of the desired pulse impedance variations A filter has been used to pass only frequencies in the pulse range but the unwanted signal amplitude was too great even in the restricted band

The time constant of the resistance coupled amplifier is necessarily large in order that the amplifier may operate efficiently at the low pulse frequencies A large signal applied to the amplifier will block it completely for several seconds while the coupling capacitors discharge to their normal condition If the unwanted signals occur at time intervals of the same order as the disabled time of the amplifier no indications will be available from the instrument This situation usually obtains when unanesthetized rats are used

Figure 27 illustrates the method of use The animal is held in the holder at the left The occluding cuff is held in position by a rod and ring stand clamp The electrodes are made of tungsten wire wound into a small helix They are attached by winding the helix around the foot and intermeshing the ends The spacing be

tween the electrodes is not critical but is usually made about one half inch The pulse indications are observed on the magic eye mounted on the front panel of the black box The pressure at which these pulsations first begin is read from the manometer to the right of the eye The chassis to the rear is the power supply

*Goldblatt* Your conclusion is that this method is good for the anesthetized animal and not for the unanesthetized animal

*Schroeder* Your method of recording occluding pressures is similar to that using a photo cell I wonder what is the advantage of this over transmitted light

*Noble* The advantage is that you can actually see the pulse With the light method it is possible that you get a low reading due to the time lag between the time the first systolic peak comes through and the time the foot fills with blood It takes an appreciable amount of blood to fill the foot and it is conceivable that a good many systolic peaks are required to produce a measurable change in the light transmission characteristics of the foot Meanwhile the pressure in the cuff is being lowered so that by the time the indication occurs the cuff pressure may be considerably below systolic

*Dole* Are you satisfied that that ring which you have for occluding the leg is effective?

*Noble* We have had plastic rings made up in various sizes to fit certain classes of animals by weight The leg is held fairly straight by means of a piece of tape attached to the tip of the foot The leg is made as nearly cylindrical as possible

*Dole* That kind of ring was one of the first compression devices introduced in human blood pressure measurements and was already abandoned by Janeway in 1901 (*The Clinical Study of Blood Pressure* 56 Theodore Janeway Appleton & Co *1904*) The difficulty is that the ring must fit with very close tolerance or pressure will be lost in stretching the internal rubber membrane before pressure becomes applied to the enclosed tissue

*Schroeder* I was interested in Mr Noble s remark about filling of the foot We have made thousands of records of direct intra arterial pressure in the femoral arteries of rats with the Hamilton manometer For routine measurements one must take the average of the highest and the average of the lowest pressures

as there is considerable variation within the respiratory cycle One also sees marked slow variations that look like Traube Hering waves under some conditions None of us using indirect methods is measuring true pressure We are merely getting the first beat that happens to come through and that may be at the bottom of the respiratory cycle at the top or somewhere between When one looks at direct tracings one can see considerable variations in the records of as much as 10 mm Hg The same thing applies in man dog rabbit and monkey as far as our experience is concerned

I wonder whether the methods need to be as exact as this when their very exactitude may give us a wrong reading Constancy and reproducibility may be more important than extreme accuracy because there are intrinsic variations from beat to beat normally Although I have had experience with the rat only under anesthesia the same applies to the unanesthetized dog rabbit and man

*Noble* It is true that there are variations from beat to beat and also variations with respiration The point which I wish to make is that we wish to obtain the systolic pressure at some instant and we wish to know we have the correct systolic pressure at that particular instant I believe that any method which does not utilize an actual pulse indication as the end point is subject to error of greater magnitude than a method which does employ such an end point If the indication is a signal at the pulse frequency there is no question that the systolic point has been reached

*Schroeder* A single systolic point it is true but is that the correct one? In man we have found systolic variations of 15 mm of mercury or more from one second to another and in a few cases of 30 mm

*Goldblatt* May I ask you your reason for not using the tail?

*Noble* In our initial experiments with previous instruments I was unable to completely occlude the artery in the tail Some pulse variations with pressures were detected even when the cuff pressure was ca 250 mm Hg Since that time we have modified the Sobin cuff and found it to obliterate the pulse signal in the tail when followed with an audible pitch variation type of signal

*Dole* Perhaps this was due to a loss of pressure with loosely fitting compression rings as mentioned before If you do calibrations as to how much pressure you need to advance the mem

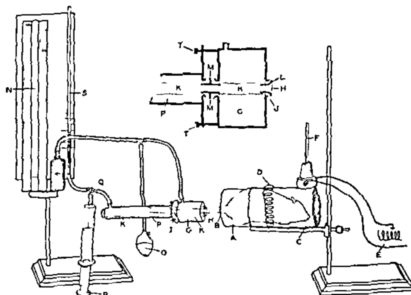



FIGURE 28 Blood Pressure Apparatus and Rat Holder* A Brass can for holding rat B Hole for rat's tail C Copper sleeve into which A slides D Heating unit from flat iron E Variable resistance F Thermometer G Pressure cuff H and I Holes through which tail is drawn J Flange to hold rubber tubing K Thin walled rubber tubing L and M Metal insert to hold tubing between pressure and plethysmograph chambers N Mercury manometer O Inflation bulb and air release valve P Plethysmograph chamber Q Three way tap R 20 cc syringe S Water manometer T Screws for holding together the plethysmograph and pressure chambers The insert shows details of construction of blood pressure cuff and plethysmograph For further details and operation see text

brane from some rigid preconstructed ring to a certain internal cylinder you find you can dissipate a considerable amount of pressure This is why human blood pressure is measured by a wrap around rather than a pre made affair In calibration experiments with lucite rings supporting internal rubber membranes similar to the ones you have used I found that it required 15 to 30 mm Hg pressure to advance the internal rubber membrane only a millimeter If you had two or three millimeters gap between ring and tail this might account for the high apparent pressures required

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*Reproduced from the original article of Williams Harrison and Grollman in the *J Clin Investigation* 18 374 (1939)

for occlusion since the actual occluding force could have been much less

*Goldblatt* I think there may be another reason Dr Dole If you have dissected the caudal artery of the rat and have studied its anatomical location you will realize how well protected it is I am not surprised to learn from Mr Noble that it is difficult to completely occlude it

Does anybody have another method which he would like to present to this group? How about the plethysmographic method on the tail Dr Grollman?

*Grollman* The original procedure described for determining the blood pressure of the rat (Figure 28) does meet your requirements namely that it can be used on the unanesthetized animal It can be used repeatedly daily or several times daily until the animal dies of old age I have taught technicians how to use the apparatus They utilize the procedure with little difficulty

There are other points which have been raised previously which I think I might mention Our aim has been to try and devise a useful procedure avoiding all obviously error inducing manipulations such as overheating exciting etc We first compared the pressures obtained by this indirect method on the anesthetized animal with those obtained by a cannula inserted in the aorta and got identical readings For that reason we thought we were getting a measurement which was reflecting conditions occurring in the circulation We also found as has been pointed out that the rat had to be kept under certain conditions It ought not to be incarcerated and restrained for a long period As a matter of fact a rat will often die if restrained too vigorously They are placed in the warm box for just a few moments The blood pressure is reasonably constant over quite a range of body temperature The latter must rise several degrees before it will affect the blood pressure Thereafter one observes a very precipitous rise in blood pressure with increasing body temperature until the animal dies from overheating We prefer to place the animal in the box till it is warmed up sufficiently to allow us to make a reading rather than warm the tail alone With this method one can obtain 30 or more determinations per hour

Figure 29 shows the type of results cited in our original paper presented a decade ago [Williams J R Jr Harrison T P

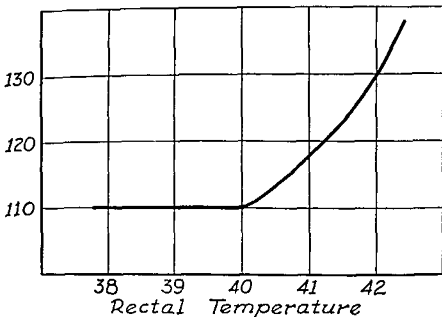



FIGURE 29 The Effect of Increasing Body Temperature on the Blood Pressure It will be noted that there is a restricted range of body temperature in the rat over which the animal may be heated without increasing the blood pressure When this however is exceeded the blood pressure rises abruptly to fall when the animal collapses as a result of heat prostration To avoid abnormally high values increases in body temperature must be avoided

and Grollman A *J Clin Investigation* 18 *373 (1939)*] These are readings taken daily on a series of five rats The spread of the readings compares favorably with direct measurements from the aorta with the mercury manometer I think they represent the median pressure We have applied this procedure to various problems in hypertension and as far as I know have never obtained any results which in the end differed from those obtained in other species namely in the dog rabbit or even in man To illustrate its use in Figure 30 you will see the type of curve you get here taking the average of five rats [Grollman A and Harrison T R *Proc Soc Exp Biol & Med* 52 *162 (1943)*] These curves are based on averages and permit one to draw certain definite conclusions

The curve in Figure 31 illustrates the effect of gestation taking pressures over a long period [Grollman A *Am J Physiol*

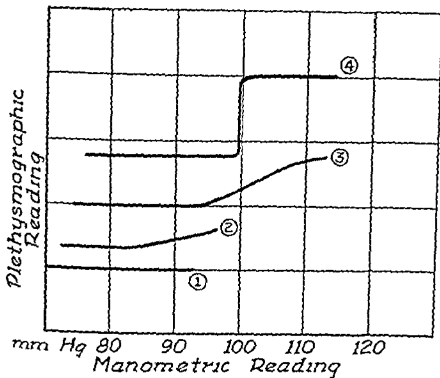



FIGURE 30 The Rise in the Column of Fluid in the Plethesmograph of the Apparatus *shown in Fig 30 with Increasing Degrees of Heating the Animal* Curve 1 shows the failure of the column to rise with minimal heating Curves 2 and 3 show a moderate continuous rise when the animal is inadequately heated Curve 4 shows the type of curve obtained when the animal is adequately heated and the correct value is obtained It will be noted that the column of fluid in the plethesmograph manometer rises with no further drop in pressure in the mercury manometer which is taken as a criterion of adequate heating

151 *373 (1947)*] These are examples of the type of results obtained on a series of 12 rats [Grollman A and Harrison T P *Proc Soc Exp Biol & Med* 60 *52 (1945)*] You get a smooth curve when pressures are taken as in this case every other day It seems to me that this is a simple procedure and as far as one can tell from the results comparable with other methods It does not allow one of course to measure the dynamics of the circulation as in the apparatus described by Mr Noble this evening but it does allow you to measure daily changes in blood pressure which reflect significant biological functions of the organism

to leave out the hypogastric which branches off in between That is why you may not be getting the same value you would get by putting a needle in the femoral without compressing it Still Dr Goldblatt s point is well taken The identity of the two pressures is a matter of coincidence and not a verification of the method

*Katz* Dr Cournand and I are worried about the fact that in the femoral artery and perhaps in the tail you should find a higher systolic and perhaps diastolic pressure than in the aorta

*Cournand* Systolic higher and the mean the same

*Wakerlin* Another feature which should be emphasized here, Mr Chairman is the use of a transparent chamber for these rats With a glass chamber or lucite chamber you see what your animal is doing

The rat is not as apprehensive as he is in the closed chamber and in view of Dr Zweifach s comments, it is probably important from the standpoint that in the light he may be less active than in the dark

*Goldblatt* Dr Haas and I have used a lucite chamber as part of a method which did not prove satisfactory although the chamber did

*Grimson* Don t you think we ought to congratulate Dr Grollman on his method which incited a tremendous amount of good criticism but which he uses despite the criticism? We do use it in principal even though we have considerably modified the apparatus

*Fremont Smith* The fact that the pressure as measured in the tail coincides with the aortic pressure consistently means that there is a continuous relationship between the two It can serve as a standard although not an absolute standard

*Wakerlin* A correct relationship because the systolic pressure in the tail should be equal approximately to the mean pressure in the aorta

*Goldblatt* Dr Page will you tell us about your method for taking blood pressure in the rat?

*Page* Dr Olmsted in our laboratory developed the method It may be of some value because of the graphic and repeated rapid

blood pressure recordings made possible We use a Brush recorder because it has the best frequency response of any of the ink oscillographs and use it routinely with the Lilly direct manometer Into the recorder we put an ink cuff pressure recorder from zero to 220 mm Hg writing almost simultaneously with the Brush pen

We place the rat in a restrainer similar to Kersten's clamp its foot at the metatarsal area to a platform by a strip of cloth running down a slot in the platform to a 16 ounce Statham strain gauge and run the gauge output through an amplification system to the Brush penmotor The circuit is designed to filter out many of the respiration and movement artifacts Would you comment on that Mr Noble? You visited our laboratory and saw the apparatus in operation

*Noble* Since the arterial pressure varies with time the arterial volume and consequently the foot volume also vary with time The volume variation causes a periodic change in the thickness of the foot If the bottom surface of the foot is firmly supported the volume variation may be detected by measurement of the displacement of the top surface of the foot When the arterial blood supply to the foot is occluded the foot volume will cease to vary with time and the periodic displacement of the top surface will cease As the pressure in the occluding cuff is lowered eventually a point will be reached where sufficient blood will pass beneath the cuff at each beat to cause measurable displacements of the top surface It is important to consider the fact that work is required of the vascular system to displace the top surface against the effective spring constant of the displacement measuring device This means that this instrument will always yield end points which are intermediate between systolic and diastolic pressure The amount by which the readings will be below systolic depends upon the pressure time wave shape and will be greater with increasing sharpness of the systolic peak The instrument probably reads a pressure which is related by a constant to the average pressure This constant is determined among other things by the initial force placed upon the foot by the displacement gauge

The average pressure is proportional to the area under the pressure time curve Equal areas may be generated by any of a very large number of different pressure shapes which may operate between widely different systolic and diastolic values If the systolic pressure is taken to be indicative of the presence or absence

of a hypertensive condition, it follows that a device which yields average pressure will not indicate such a condition because neither the systolic nor diastolic pressures can be determined from the average pressure unless the pressure time wave shape is known This wave shape cannot be determined by the use of this instrument alone

If the pulse pressure is small i e if the difference between systolic and diastolic pressure is small then the average pressure becomes more nearly a measure of systolic or diastolic pressure whichever is desired The accuracy obtainable from an average pressure reading depends upon knowledge of the order of magnitude of the pulse pressure

When this instrument is used with unanesthetized animals, spurious displacements of large amplitudes often occur due to motion of the animal These displacements may be of the same or greater order of magnitude than the displacement due to the pulse This means that the desired end point may be more or less completely masked by the undesired displacements An attempt is made to filter out the undesired displacements by the use of electrical circuits in the recording equipment The method consists of lowering the high frequency amplification by connecting capacitance to ground in the coupling circuits of a resistance coupled amplifier This produces in effect a broad low pass filter Since the undesired displacements contain large bands of frequencies it follows that such a filter will discriminate to some extent against high frequency components in the undesired displacements However there are still large components of undesired displacements in the pass band

I had an opportunity to observe the operation of this instrument for a brief period The animals were unanesthetized The records obtained in every case were so masked with extraneous displacements that the end point was subject to opinion I am not in a position to state that the instrument is not satisfactory because I have not observed its operation over a sufficient period to reach such a conclusion However from my limited observation the shortcomings enumerated above are very much in evidence

*Page* The pulse can readily be obtained in the anesthetized rat and with some trouble in the unanesthetized By watching the ink pulse recording and at the appropriate time (when the pulse

is recording clearly) inflating and slowly deflating an occluding cuff on the rat's ankle (and that is the only place a cuff will stay on a rat's leg) we can obtain a systolic pressure on a permanent record

We have compared the method with the Hamilton manometer over a wide range There is some discrepancy when you get down around 50 mm Hg and when the pressure is around 200 it again skews a little The average comes out around 7 mm lower than carotid pressure The rats have to be trained in a holder for half an hour for three days On the fourth day the pressure can be taken

We have found that the rat's blood pressure is more labile than we originally thought The pressure goes up on heating to 140 150 the first minute and then begins to drop back and after three or four minutes to around 110 or 100 mm Hg Our feeling in general is simply this if one is willing to accept wide variations in blood pressure in your experimental data there is no objection to using the original method

We heat the whole rat or the room Personally I am inclined to prefer the heating of the whole room so that the animal lives in a room with a high temperature I am unable to demonstrate the precise value of this alternative but it eliminates the problem of heating the rats just before taking pressures I think it depends on whether you are willing to accept wide variations in pressure in your hypertensive experimental data

In short either the heating of the tail or the whole rat can be used The only objection we have to the heating of the tail is that it is time consuming

I should add that our present method is still a bit tricky to use and requires a very careful technician

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*Goldblatt* Our next topic on the program is a discussion of congestive heart failure by Dr Stead

# CIRCULATORY FACTORS IN CONGESTIVE HEART FAILURE

EUGENE A STEAD Jr
*Department of Medicine Duke University School of Medicine*

Circulatory factors in congestive heart failure is a very general topic I would like in the beginning to draw your attention to certain parallelisms between the phenomena of congestive failure and those of shock With very few exceptions, the discussion of one phenomenon can be transposed almost entirely to the other phenomenon

The clinical picture of chronic congestive heart failure has changed over the period of the last four or five years Formerly most people who were in heart failure and stayed in heart failure presented the clinical picture of waterlogging Now by the persistent use of some kind of a de salting mechanism or by *not* giving these people any salt we have large numbers of people with heart failure who show remarkably little congestion and who on simple inspection give no evidence of heart failure The hemodynamic studies of such individuals will show that they have all the circulatory disability which is present in a patient who is short of breath or orthopnic edematous and in obvious failure The portion of the picture which is due to the large accumulation of salt and water has been lost This has produced some difficulty in the interpretation of reports in the literature because of the use of the terms compensation and decompensation Cardiac patients who have lost their edema will fall into two groups those who have had actual improvement in what their hearts can do and in that sense are compensated in the way the term is usually used and those who are symptom free at rest because of loss of congestion but without any increase in the amount of blood pumped per unit of time

We will run through some of the abnormalities of the circulation in congestive heart failure The first one has to do I think with the cardiac output As you know the reserve of cardiac output lies in the direction of doing more The amount which the cardiac output can be increased above the resting level is much

greater than the amount which it can be decreased below the resting level At the start of studies on patients with congestive failure we felt that it might be impossible to demonstrate at rest a consistent change in cardiac output just because we were working on the wrong end of the curve It does turn out though that the output is demonstrably lower in that group of patients who have chronic congestive failure without complicating disease By our definition the patient who because of cardiac disease develops edema at bed rest on a normal diet is in chronic failure It is obviously an arbitrary definition of chronic congestive failure Nevertheless if one does use it in this way one finds that the cardiac output data and the clinical evaluation are surprisingly consistent and that the great majority have an obvious decrease in the resting cardiac output Most of those with border line normal outputs can be slowed to subnormal for that particular individual by demonstrating on digitalization a rise from low normal values to average normal values So I think we can say that in uncomplicated failure the patient who at rest and on a normal diet exhibits abnormal retention of salt and water has a low cardiac output There has been much emphasis put on the situation in which the cardiac output at rest is greater than the expected normal resting level These patients have been picked out for special comment because they are supposedly rare It is certainly true as we have said that if you study the folk with failure at rest one finds the low output On the other hand if one studies the natural development of congestive heart failure the situation is quite *different* *Here you* have individuals who have normal outputs at rest but who during the course of the 24 hours have hearts which do not respond normally Therefore we have the situation in the early stage of congestive failure where the man doing his work develops congestion while his cardiac output is considerably above that which is present when he goes to bed at night He will give you the characteristic story of decompensation during the daytime He has oliguria and edema during the day and has to get up at night to void because his circulation at rest is normal We have the usual picture of decompensation with the output above the resting level during the day and compensation at night with a lower output So that actually the development of congestive failure with an output above that which is present in a normal subject lying in bed is the rule and not the exception The only exceptions to low output failure at rest are in those individuals in whom the

cardiac output is normally above the basal level These are patients with anemia AV communications thyrotoxicosis beriberi and anoxia The output will usually be above the normal resting value when the manifestations of congestive failure occur

The primary difficulty seems to be that the heart does not pump enough blood for any given state of body activity to distribute this blood throughout the body in a way which satisfies the entire organism and certain changes occur which we call congestive failure The peripheral resistance is increased as the cardiac output falls so that the blood pressure is well maintained The amount of reduction in cardiac output and the ability to maintain a relatively normal blood pressure makes the cardiac patient differ from most experimental preparations which are made in the laboratory Congestive heart failure does not cause a lowering of arterial pressure We would of course like to know why this increase in peripheral resistance occurs We get back to the old business that it might be the result of humoral or reflex mechanisms or both If one begins to analyze the areas in which the constriction occurs one finds that there is a widespread constriction of the entire vascular bed on the arterial side The areas which have been studied in some detail are those of the kidney the splanchnic region and the brain In the splanchnic area and in the brain the reduction in blood flow is proportioned to the reduction in cardiac output in the kidneys the decrease is greater than the reduction in output

If you know the fall in cardiac output you can predict pretty well the blood flow through the head and the blood flow through the splanchnic area For reasons not at all clear to us this situation does not hold in the kidney As you know renal vasoconstriction is a striking and constant finding in chronic congestive failure which fits the particular definition we have given and this vasoconstriction is out of proportion to that which is present in other organs This pattern of constriction seems to be characteristic of a reduction in cardiac output and it is identical with that which is observed in decreased cardiac output from such simple phenomena as hemorrhage

One then passes on to the venous system We feel there is the same evidence of constriction present in the venous system that is present in the arterial system In patients with congestive failure of longstanding duration there is an increase in venous pressure

It appears that this increase in venous pressure has at least two mechanisms responsible for it The first of these is an increase in blood volume In the patients with chronic heart failure, this is by far the easiest of the variables in venous pressure to analyze A number of variables have dropped out of the picture if one selects this particular group of patients with chronic failure For example changes in the cardiac output are nearly eliminated These people have low cardiac outputs all day long and their output increases remarkably little on attempting exercise If you push them very much they will decrease so that the variable of a changing cardiac output is nearly eliminated One is working with a relatively fixed preparation as regards cardiac output The venous pressure seems to vary directly with the blood volume If you lower the blood volume the venous pressure drops If you raise the blood volume the venous blood pressure goes up The second method of varying the venous pressure is by changing the venous tone There is some evidence that a reduction in cardiac output causes an increase in the tone of the venous system We have known that the venous system can increase its tone because of the experiments of various people with drugs If you give drugs as paredrinol or neosynephrin the venous pressure will rise without any change in the blood volume The veins are able to constrict sufficiently to vary the central venous pressure over a fairly wide range It is very common of course in congestive failure to find the two mechanisms operating together If one digitalizes a patient with failure who is capable of responding to digitalis and has a high venous pressure a relatively immediate drop in venous pressure will occur and this drop in venous pressure has nothing to do with changes in plasma volume The decrease in venous pressure may be a direct effect of the drugs on the veins or it may be the result of the increase in cardiac output If the patient is edematous the venous pressure on digitalization usually falls to a level which remains considerably above normal As diuresis occurs and the blood volume falls the pressure reaches a normal value

*Fremont Smith* Do I understand when you give digitalis to such a patient that you get a drop in blood volume?

*Stead* You get no change in blood volume

*Fremont Smith* You get a drop in venous pressure without any drop in blood volume and then with diuresis you get a fall in blood volume?

*Stead* Yes

*Katz* Is it not true that digitalis will produce a similar drop in venous pressure in the normal person?

*Stead* It certainly does though not of the same order of magnitude

*Katz* While there is no shift with digitalis between the blood and the extracellular space there is a shift between the blood in active circulation and blood in reservoirs, or don t you agree?

Furthermore, just to bring out the other possibility most people who have seen patients in chronic congestive failure are impressed with the fact that the visible veins seem to be unduly distended for the existing venous pressure Have you any evidence of a direct nature like a P/V ratio to show an increase in veno motor tone?

*Stead* Dr Katz the questions you raise are very good ones and I cannot answer them I am not impressed with the segregation of blood in patients with chronic failure or in normal people The reservoir mechanism does not seem to be as well developed in man as in the animal

I think the point you have raised the fact that the jugular vein can be very dilated and still all the other veins hard to find is a fairly common one The impression I have is that the small veins do the constriction and the bigger veins do the holding A vein the size of the internal jugular would probably not be the one in which this increase in venous tone operated but there is no proof at all of that

*Katz* I think you have described the situation beautifully as far as the small and large veins are concerned in regard to their assuming a true blood reservoir function Why not admit a similar situation between the hepatoportal system and the rest of the venous system?

*Stead* The only question is whether blood is circulating through all of these veins

*Katz* The hepatoportal system is like a lake With the Hoover Dam damming up is present but there is still flow

*Stead* There is blood within the venous system which can be pushed toward the heart without contraction of the heart

*Cournand* If you assume that the method of determination of blood volume by T 1824 and hematocrit is approximately correct then we have considerable data to prove that there is no change in blood volume during acute digitalization while there is a significant change in cardiac output and central venous pressure

*Fremont Smith* I am not certain of what the word acute means You mean prior to diuresis or including the period when the individual has diuresis?

*Cournand* The patient is studied for 1½ hours after intravenous injection of digoxin 1 to 1½ mg The blood volume is taken before the diuresis

*Katz* Don t you think the work of Wollheim is upsetting? He supposedly measured the circulatory volume and reported a contrary finding with digitalis

*Cournand* We have been using a method for blood volume determination which is considered at the present time as fairly accurate and we have found no changes

*Lamport* Dr Stead are you referring to peripheral venous pressure? Did you measure it in the antecubital vein or at the heart which would be central venous pressure?

*Stead* In these individuals who have sufficient blood volume to distend the venous system it does not make too much difference You get the same general order of finding These happen to be right atrial pressures

*Perera* When you say no change in blood volume can you exclude a redistribution a shift from the venous side to the arterial or capillary reservoir? The overall blood volume may remain the same

*Stead* It is certainly possible that there are shifts in blood and that is one of the possible explanations for changes in venous pressure If one reviews the total evidence for the venous system constriction it is reasonably impressive All we know is that the pressure being relatively high in the arterial system and remaining relatively high as the patient is digitalized I would say the shift is not in the arterial system It does not seem to be from the heart We don t have any observations of the pulmonary distribution in digitalization Dr Cournand might be able to tell us how much blood shifts out of the lungs under those considerations

*Cournand* I don t think there is any valid method to date to measure lung blood volume in spite of a recent paper to the contrary As long as the mean circulation time from the pulmonary artery to the pulmonary vein remains in doubt the exact volume of blood in the lungs cannot be calculated In the new technique proposed based on the injection of dye into the pulmonary artery and the collection of samples in a systemic artery only the volume of the blood from the pulmonary artery to the point of sampling can be estimated The largest error in estimation comes from the unknown volume of blood in the left ventricle

*Lamport* I don t see why constriction of the veins will necessarily increase venous central pressure On a dynamic basis it seems to me that constriction might increase to some extent the hindrance of the veins It might thereby raise capillary pressure due to an increase in pressure drop from peripheral veins to the right auricle but the pressure in the auricle might still be normal I think you could set up a system on paper at least where the central venous pressure was not changed it would involve some redistribution of blood To ascribe as the primary motivating agency a constriction in the venous side does not seem to me adequately reasonable

*Fremont Smith* There are two factors During a period of active constriction of the veins they could push more blood to the heart Once the veins have become constricted and are stationary then they would serve to increase resistance to flow through them One therefore must distinguish between the change in tone of veins to a constricted state and the status that exists after they have become constricted I think that between those two Dr Lamport your situation prevails

*Lamport* Probably Paredrinol in the normal person will raise the venous pressure by constricting the veins (8) *

*Stead* We are dealing with a situation in which the circulation is running round and round and the heart is sitting in the middle and making the blood twirl

Dr Starr pointed out some years ago that you had a system of a given capacity with a certain amount of fluid in it flowing at

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*See Page 131

a certain rate and that one could raise the pressure of the venous system over a rather wide area by increasing the volume without necessarily changing the amount of blood flowing round the circle To this he gave the name static venous pressure and it is certainly true that one can by a drug as paredrinol (neosynephrin is even a little better) produce very striking rises of venous central pressure without rises in cardiac output

*Cournand* In fact the drug may cause a drop in cardiac output

*Ogden* Do these drugs have any effect on the pulmonary arterial vessels?

*Cournand* The systolic pressure of the right ventricle goes up At the time we studied these drugs we measured only the right ventricular pressure We have no information as to the changes in diastolic pressure in the pulmonary artery

*Ogden* I am raising the question as to whether you get a change in central venous pressure Is it because of what the paredrinol is doing to the veins or what it is doing to the pulmonary arterial system and backing blood up?

*Cournand* I would even say what it does to the systemic circulation as a whole because all parts of the circulatory system are tied together With increasing peripheral resistance we have some proof that changes in the pulmonary circulation might be observed

*Bradley* You can have an increase in the venous pressure with the cardiac output changing in another direction with neosynephrin

*Cournand* With angiotonin and paredrinol there is a drop in the cardiac output and the central venous pressure goes up

*Schroeder* Time relations are extremely important here Could you enlarge on that a bit because Dr Cournand did not quite answer it? There is always the possibility which has not been disproven that digitalis acts directly on the kidney as well as on the heart

*Stead* We have never obtained satisfactory data on the actual time relationship Dr Cournand may be able to answer that.

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*Stead* We have never obtained satisfactory data on the actual time relationship. Dr Cournand may be able to answer that.

*Schroeder* If diuresis starts at all, the fluid does not have to lower the blood volume

*Stead* I think it does

*Katz* I would like to see how Dr Lamport would respond to this If you have a pump in the system with pressure behind it that pressure would be determined by the pump s ability to empty the blood that comes to it In other words in a system of hydraulics with a pump the pressure behind is a measure of the pump s capacity to drain out the blood coming to it Therefore it implies ability to handle increased or decreased flow of blood to it This is raised to counteract Dr Stead s argument

*Stead* Let me give you one more set of data There are many situations in which the relations between atrial pressure and cardiac output are not simple One of those is by simply raising the blood volume By giving a large amount of albumin in blood one can raise the atrial pressure to a considerable height The response of the circulation to such infusions is extremely variable and is difficult to relate to atrial pressure changes Similarly one can lower the atrial pressure within certain limits by taking out fluid without causing a consistent fall in atrial pressure

*Katz* When one uses a drug one must consider its effect on the specific contractility of the heart The mere fact that cardiac output does not change and that venous pressure rises might still mean that the heart is a poorer pump and requires a higher pressure to maintain the same output The same mechanism holds as regards carbon dioxide tension and respiration Dynamically stated carbon dioxide tension may not change but there is increased respiration It is not enough to measure cardiac output or venous pressure Some measure of the heart s ability to empty under different circumstances must be considered

*Fremont Smith* Along that line isn t one of the most characteristic reactions of the normal heart the ability to respond with increased output to increased inflow (venous return) and therefore if it does not so respond one has to raise the question clearly has something happened to the heart?

*Stead* It depends upon how you look at the circulation You probably know I always look at things upside down So I look at the circulation upside down Dr Katz of course has put the

finger on the answer to all our problems Actually the control of the circulation in normal states is vested in the ventricular muscle and for any given set of filling conditions the output of the heart can be varied tremendously by factors acting directly on the ventricle itself

I think in normal physiology we are forced back to the conclusion that the active thing determining the amount of blood which is being pumped under any given set of circumstances is the ventricle It controls its own fate to a very large degree and is much less passively controlled by the venous and auricular factors than is generally thought

*Fremont Smith* May I add one more bit of philosophy? I don t think there is any implication that the heart is passive merely because it responds to increased venous flow There are a number of mechanisms which could stimulate the ventricle to react actively

*Stead* I think it is perfectly true that the reserve is upward but I would have said that its reserve the active portion of the system concerned with pumping blood is in the ventricle and that under some circumstances it regulates its own output

*Bozett* See whether you accept this as another way of wording it The Starling law works but as the last line of defense and not the first Only after you have exhausted the other methods of doing it are you forced to use that as your last line of defense and if that fails you are on the downward grade?

*Stead* If you push it back of course to the things which I still think Starling studied primarily viz cardiac outputs below the normal level then I think one finds a very close correlation In simple hemorrhage one at first finds the atrial pressure takes a sharp drop without a corresponding change in cardiac output and then if bleeding continues, there comes a time when the circulation calmly fades away without any further easily determined fall in actual pressure When one gets to the lower end of the scale one certainly obtains data fitting the Starling phenomena When one gets into heart failure I am a little less sure of it

*Fremont Smith* What about the filling pressure?

*Stead* It has been shown by a number of people that in

chronic heart failure, the heart does less well if pushed The normal individual increases his cardiac output with exercise The cardiac patient may have some increase in output but if exercise is continued the cardiac output may begin to fall Two interpretations are possible It depends purely on the point of emphasis which you like to make Dr McMichael has said that the heart is overextended by filling pressure At this particular time we would have said the primary difficulty of this heart is not difficulty in filling It is too big anyway Before the start of exercise, the primary difficulty of this heart is to empty As one pushes the heart and makes it empty more one gets into simple muscle fatigue phenomena and in due time the cardiac output falls We would say there is as yet no evidence in man that there is an acute over distention of the heart at that particular time Again this has to do with the emphasis which one puts on the ventricular side of cardiac output control as contrasted to the more passive control from the atria So we have the same observed facts from several laboratories and we end up with very different interpretations

*Goldblatt* Is there any information about the coronary circulation in the distended human heart as opposed to the normal heart?

*Kety* Richard Bing has made such observations in congestive failure with the nitrous oxide technique He found I believe that coronary blood flow and myocardial oxygen consumption were relatively normal but since there was a decrease in cardiac output and in left ventricular work he calculated a marked reduction in the mechanical efficiency of the heart

*Cournand* The whole being based on coronary flow per 100 grams of heart

*Kety* That is perfectly true but his error would be to over estimate the efficiency in congestive failure on that basis Since he could not weigh the heart in congestive failure he assumes it to be normal

*Katz* If the heart lung preparation can be brought up we found that when cardiac output was artificially kept steady, the coronary flow tended to increase as heart failure developed

*Stead* We of course are left with questions in regard to venous pressure Noting Dr Katz s objections and still holding for

the moment to the same line of thought an analysis of the venoconstrictor mechanisms and of the things which increase the plasma volume seems to be in order Our own feeling is that the plasma volume changes are the easiest to understand and we would have guessed that as the extracellular space increases with the retention of salt and water the blood volume increases as part of that retention (it is after all a portion of the extracellular space) As the plasma volume increases the protein concentration decreases This fall in the amount of protein per 100 cc of fluid serves as a stimulus to cause increased protein production This makes the mechanism of the increase in blood volume relatively simple

*Fremont Smith* The increase in blood volume being due to the increased protein?

*Stead* Congestive failure is an extremely interesting situation It is one of the few situations in which you get a large blood volume and a high capillary pressure and a chronic state There is plenty of time in congestive failure for everything to come into equilibrium One of the things which puzzled us in our beginning studies of congestive failure was the high capillary pressure and large blood volume present at the same time One day we attempted to produce congestive failure in the laboratory Since the edema of congestive failure was thought to be the result of increased venous pressure one could get increased venous pressure in two-thirds of the body by leaning up against the wall Dr Ebert and I reclined against the wall and drank large quantities of normal saline Sure enough we increased our weight with the fluid intake of some three to five liters Under such circumstances one will void only about 150 cc in 8 hours If one has the ability to really stand still one can have the phenomenon of fluid retention On the other hand we never got the blood volume back to the pre standing level It fell as soon as we assumed the standing position and though we increased our weight we were never able to increase the plasma volume We could not drink rapidly enough to counteract the effect of gravity

In chronic failure the sequence of events seems to be as follows After a variable period of retention of salt and water—and this period of time depends I think solely on how well nourished you are—one reaches the point where it is difficult to pack

more fluid into the tissues and the tissue pressure begins to rise When the tissue pressure rises the retained salt and water enter the tissue spaces less easily and one gets a further increase in blood volume and a little increase in venous and capillary pressures The more fluid retained the greater the tissue pressure and the greater the increase in blood volume As this is going on one has a drop in plasma protein concentration and we have always assumed that this was the stimulus for making more protein Be that as it may the cardiac patient makes more protein as he goes into congestive failure His liver works well enough to pour the protein out It comes out in the first few days in quantities comparable to those mobilized by hemorrhage

*Katz* Has anybody been able to produce true chronic congestive failure in any experimental animal by any technique? We have tried for years and have failed utterly

*Stead* I have heard of congestive failure occurring spontaneously in animals I have never seen it As far as I know it has never been produced It may be related to the greater ability of many animals to excrete salt

*Schroeder* Could I give you our experiences? We have burned the ventricles of dogs with a soldering iron We have then increased cardiac output by producing neurogenic hypertension In the same dogs we have taken out one kidney we have given 30 grams of salt a day and we have implanted DCA pellets and we have tied off half the blood supply to the remaining kidney The dogs still don t show more than transient small increases in body weight for a week and then diuresis

*Katz* We gave dinitrophenol injected occlusive particles into the coronaries etc and we failed

*Dexter* Poos in St Louis reported that the intra aortic injection of a fine suspension of potato starch into the proximal aorta embolized the coronary circulation and produced congestive heart failure in dogs

*Wakerlin* I understand in Visscher s laboratory they have in the last year produced chronic myocardial failure in the dog by combining large arteriovenous fistulae with administration of salt

plus adrenocortical hormones As far as I know it is the first instance in which chronic myocardial failure has been produced in experimental animals in spite of a vast number of experiments by various investigators

*Schroeder* Poos and Smith produced acute failure in intact dogs We have used the same technique in an attempt to cause chronic failure and were not able to do it The aorta is suddenly clamped the starch injected into the arch 3 or 4 beats allowed to pump it through the coronaries and the clamp released It has been my understanding that heart failure has been produced before by the production of arteriovenous fistulae but we did not think that was quite a fair duplication of the clinical state

*Katz* We have had chronic congestion in pericarditis There is little reason to believe myocardial incompetence is part of this picture I think it is vitally important to elucidate Stead s beautiful ideas in experimental animals Hence the need to induce experimental chronic congestive failure due to myocardial incompetence

*Bazett* The protein picture and blood volume appear to be to some extent an exaggeration of a normal relation that Dr Stealman described He demonstrated with normal subjects lying down for as little as four hours the reduction in blood volume that Ancel Keys described with prolonged bed rest The secret of the analysis is the differentiation between changes in fluid content which are relatively temporary and alterations in the total plasma protein in circulation (not its mere percentage concentration) which modify conditions of osmotic balance

On normal subjects he could show a decrease of some 10% in blood volume on the assumption of a standing posture as the result of mere transfer of fluid into the tissues as blood tended to pool in the lower parts of the body However this tendency to reduction in blood volume was counteracted gradually by an immediate increase in the formation of plasma protein so that the total amount of plasma protein in circulation (calculable from plasma volume and protein concentration and not from concentrations alone) becomes greater An average subject will have about 200 grams of circulating plasma protein but this amount is reduced by about 20 grams during rest in bed every night and is increased by the same amount during the day s activities This increase in

plasma protein during the day tends to counteract the loss of fluid from the blood and to make the reduction in blood volume on standing less than it would otherwise be Consequently by the evening the total blood volume may be less than it was at the start of the day but the quantity of plasma protein is considerably increased When the subject resumes a horizontal position a larger volume of fluid is reabsorbed from the tissues than that originally extravasated so that the blood volume is supernormal for this posture During the night the removal of plasma protein allows the blood volume to be again reduced The changes can be demonstrated to depend mainly or entirely on posture and to be reversible within a few hours as the posture is changed

There is abundant evidence that diurnal changes in hemoglobin and plasma protein concentrations are exaggerated in cardiac patients particularly those not far removed from decompensation Isn t it probable that such patients during exercise in the daytime need to maintain venous return to the heart more effectively than does a normal subject Let us assume that blood volume reductions on standing are more than ordinarily compensated by new formation of plasma protein to make this adjustment As soon as the subject lies down he has a supernormal blood volume, with an increase greater than that of a normal subject Yet he has a subnormal capacity to deal with an increased venous return by an increased cardiac output The cardiac starting decompensation is in a difficult position He cannot do exercise in the vertical position without preventing the normal reduction of blood volume on standing to an exaggerated extent He must maintain venous return Yet on return to a lying down posture he has too large a venous return due to a supernormal blood volume and this imposes a new strain on the heart in its turn Thus he is between the devil and the deep blue sea

One issue I want also to bring up is the possible mechanisms involved in the protein increase I was prepared to explain Spealman s increase as a compensation to the pooling of blood in the legs on standing Spealman countered that in that case it should not happen if a subject sat up in bed without his legs being lowered I considered that the absence of change under such conditions was so certain that the experiments were hardly worth carrying out Dr Spealman carried them out and the changes in the total plasma protein were not only demonstrable but possibly

just as great as those observed during the full postural changes of standing On such grounds Spealman formed the hypothesis that protein was formed in response to some balance between plasma protein concentration and pressures in the hepatic veins He tried experiments involving compression of the inferior vena cava with metal loops, but no definite evidence was obtained either for or against the theory I mention the theory of his only because it could be of immense importance in understanding congestive failure if it should prove to be correct

*Shorr* What evidence is there of protein destruction?

*Bazett* We were measuring blood volumes night and morning daily or every other day with carbon monoxide and estimating the total plasma in the body from plasma concentration and plasma volume deduced from blood volume by hematocrit measurements

*Shorr* Does it come out in the urine as nitrogen?

*Bazett* We have not investigated the nitrogen story The point he tried to argue was that the formation of protein was controlled by a balance of plasma protein concentration versus pressures in the hepatic system

*Stead* I am not sure about the actual factual material I would like to review the actual experimental data before saying it

*Bazett* But the protein circulating has been getting larger because your plasma protein concentration is rising more than would occur from mere loss of fluid You can prevent reduction in blood volume in the vertical position only by increasing the colloid osmotic pressure You can do it and I bet you are doing it now

*Fremont Smith* You are saying although the blood volume is going down during the period of standing he is beginning to build plasma protein in order to bring it back again?

*Bazett* Spealman compared blood volumes measured by carbon monoxide on the same subjects lying in the morning standing up in the morning for 20 minutes and lying down at the end of the day The morning standing for 20 minutes reduced blood volume without measurable changes in total hemoglobin or plasma protein At the end of the day with the subject lying down the blood volume was increased as the result of an increased quantity of plasma protein (in grams) When standing at the end of the

day these two opposite changes would be more or less balanced The rates of change were followed out by systematic comparison of changes in hematocrit and hemoglobin concentration with those in the concentration of plasma protein The data demonstrating the increased plasma protein at the end of the day were reported in the *American Journal of Physiology* 150 *628 1947*

*Stead* I don t want to belabor the point, but I would like to point out this is measuring a shifting system of tremendous complexity For example if during a 20 minute period of time one samples hematocrit from veins ranging from head to foot one finds a progressive change Eventually this system can be gotten into equilibrium If one has an increase in capillary pressure in the portion of the body long enough it balances off sufficiently with tissue pressure so that the whole edema cycle is stopped

*Wakerlin* May I ask if Dr Katz would brief us on the techniques he used in trying to produce experimental chronic myocardial failure in dogs?

*Katz* We have injected large and small particles into the coronary arteries We have made valvular insufficiencies We have produced stenosis of the aorta and partially tied the main pulmonary artery We have produced pulmonary emboli of various types and allowed the animals to survive We have fed thyroid and simultaneously produced hypertension We have also used dinitrophenol We have tried DCA and large fluid loads Yet we have not found anything that looked promising

I think that the importance of solving this experimental state of chronic congestive heart failure is illustrated by the advantages of the Goldblatt era in hypertension

*Ogden* I would like to raise this question About 10 years ago George Fair did some work on acute experimental heart failure with diphtheria toxin I wonder whether anybody had tried manipulating the diphtheria experiments in such a way as to try to produce chronic failure

*Katz* Dr Kondo in my place tried diphtheria toxin unsuccessfully

*Schroeder* Do you know of any evidence that there is regeneration of blood during the onset of failure and blood destruction during diuresis that ought to change along with the protein?

Since the red count is approximately normal and the volume increased there must occur large changes in hematopoiesis

*Stead* One is easy to study and one much more difficult because the plasma volume changes can be made to go back and forth easily There is always a lag in the red cells The state of patients changes Methods are available to settle this point I am not willing to accept any of the data published so far as being convincing

*Bywaters* I think it should be emphasized that the plasma protein is much more likely to be stored than actually broken down I have injected 600 grams of plasma protein and the major part of that was stored almost immediately

*Fremont Smith* Where is it stored?

*Bywaters* I don t know The liver presumably

*Stead* I will finish quickly with the pulmonary circulation As you know in most types of clinical congestive heart failure there is a selective predisposition for fluid which is put into the body to localize in the lungs Take an individual who has been in good health who has had a sudden lesion involving the left ventricle give him a bit of salty fluid and you will find that he will drown very easily This abnormality in the lungs in congestive failure differentiates the usual patient with heart failure from the normal subject to whom you give fluid at a more rapid rate than he can excrete it Such a normal subject will develop edema This edema will have a fairly reasonable relationship with what we know about tissue pressure He will not have any particular predisposition to pulmonary edema If he does he is not normal We believe this predisposition for the accumulation of fluid in the lungs is the result of actual backing up of blood in the lungs behind the left ventricle and we would be proponents of the thesis of left ventricular failure The blood volume is available in the peripheral circulation to flood the lungs through venomotor mechanisms We would be rather skeptical of right ventricular failure because the aspects of drowning the whole body with the blood obtained from the lungs by venomotor mechanism have never appealed to us I would only like to say that this phenomenon of an increased capillary pressure in the lungs and the ease with which one drowns out the patient varies considerably during the period one observes the patient For example in the patient with acute failure a little

fluid will drown him out and the abnormality in the lung seems to be present there at all times It is present at any level of cardiac output which you wish to study and I think that accounts for the fact that slowing the rate of giving the fluid does not always save you from getting into trouble The abnormal capillary pressure is always present regardless of the rate at which one gives the fluid If one gives fluid at the rate which exceeds urine output one will develop edema whether or not during the injection of fluid the right ventricle output has been raised

I think the effects of poor nutrition and loss of tissue become obvious at an early date In time the right heart also begins to fail and one has a more generalized form of failure and less ability to build up an abnormal situation in the lungs Now, when one gives a large quantity of salt and water the patient will develop generalized swelling and you can put a lot of fluid into him before he drowns out Clinically of course we know these observations are of some practical use In the patient who has persistent left ventricular failure one has to be particularly careful about experiments which cause an increase in water content of the body On the other hand if an individual comes in with 40 pounds of edema and has lost it that individual is apt to be very tolerant of large amounts of fluid He may re swell but the distribution of edema is apt to be the same, and a special predilection for the lungs may not occur

*Katz* The venous pressure with digitalis goes down?

*Stead* Initially the venous pressure in congestive failure is elevated prior to digitalization This is not always true I think Dr Bloomfield and his group in Boston with the use of strophanthin obtained a sharp increase in cardiac output with a fall in venous pressure There seems to be a great deal of evidence that with a given venous pressure one can have marked variation in cardiac output

*Cournand* I cannot agree with the statement that the cardiac output will change with digoxin without any change in the central venous pressure

*Stead* I think you will have to repeat those experiments using strophanthin

*Katz* McMichael told me recently that he had confirmed Bloomfield's results with strophanthin

*Cournand* I will inject something in this connection You cannot take the central venous pressure as an indication of the variation in the filling pressure of the right ventricle I think I will have some data on this point later on

*Schroeder* In regard to Dr Stead's last point I would agree that it is very difficult to get failure of one side of the heart without failure of the other particularly in the chronic state Because of the anatomy of the cardiac musculature which has many fibers surrounding both ventricles obviously some bilateral failure is to be expected For the record we ought to remember that the same thing which we call congestive heart failure can occur from non cardiac or relatively non cardiac conditions In adhesive pericarditis the cardiac muscle may be normal the valves may be normal but there is interference with cardiac output In obstruction to the great veins from pericarditis or mediastinitis in which cardiac output is diminished the whole picture of retention of salt and water follows When there is interference of inflow through the tricuspid valves (which is cardiac in the large sense but actually mechanical) the same sequence of events occurs with a perfectly good right and a perfectly good left ventricle

I would like to go along with Starr and Dock and broaden the definition of this term to congestive circulatory failure When we confine it to the heart we are apt semantically to think of it as myocardial failure and it is not always myocardial failure that produces this syndrome

*Shorr* I wonder whether Dr Stead would mind philosophizing a little bit Ordinarily mechanisms in the body don't act without some relationship to homeostasis Why the increase in peripheral resistance in heart failure I am wondering what could be the reason what type of adaptive mechanism this might represent

*Katz* It might be simply to provide blood to vital organs since the cardiac output is decreasing Redistribution of blood is one of the reasons for vasoconstriction

*Bradley* Does the blood pressure ever fall in the course of congestive heart failure?

*Stead* Yes but usually not

*Bradley* Could you say the fall in blood pressure elicits vasoconstriction?

*Stead* The cardiac output falls It is possible that the blood pressure falls at some time but is restored to normal by the homeostatic mechanisms

*Shorr* You said at the very beginning you were struck with the analogies to shock

*Stead* I do think that the circulatory dynamics of the peripheral circulation are identical The difference in the usual clinical picture depends on 3 factors (1) increase in blood volume (2) fluid intake exceeding fluid output over a long time (3) increased capillary pressure in the lungs from left ventricular failures

*Wakerlin* Has it not been shown that the vasoconstriction in myocardial failure is not neurogenic as far as the kidney is concerned that spinal anesthesia does not increase the renal blood flow?

*Bradley* I don t think we can say with certainty that the vasoconstriction is reversible because it is pyrogenic or because vasodilatation is due to congestive heart failure

*Wakerlin* What about the report that spinal anesthesia does not increase renal blood flow?

*Bradley* The blood pressure was maintained in those experiments with neosynephrin and neosynephrin causes vasoconstriction within the kidney

I don t know that we have enough evidence to expect a vasodilatation as a result of high spinal anesthesia since in normal persons high spinal anesthesia may be induced without any change in renal vasomotion Such a change in renal vasomotion is detectable only when a further stress is imposed such as standing

*Dexter* I wonder if this vasoconstriction in the periphery may not be a general law You find exactly the same thing in the lungs Normally pulmonary capillary' pressure is in the neighborhood of 10 mm Hg as it rises the pulmonary artery pressure rises to a similar extent When the pulmonary capillary pressure approaches 25 mm Hg which is the approximate osmotic pressure of plasma the pulmonary arterial pressure rises out of all

proportion becoming extremely elevated The arteriolar resistance in the lung increases as much as 10 fold or more

*Cournand* This is in contradiction with what Visscher and his group have shown recently, although I don t doubt that you observed the changes and that your explanation may be valid Visscher in creating a condition of increased intracranial pressure and measuring pressure in the pulmonary veins in the pulmonary artery and measuring the cardiac output has shown the pulmonary venous pressure rise markedly during the development of pulmonary edema As a rule the pulmonary venous pressure went up more than the pulmonary arterial pressure in these experiments

He must have gotten a level of 20 25 mm of mercury They were very insistent on the relative pressure rise of the pulmonary vein and pulmonary artery pressure Obviously this introduces the question of the volume pressure relationship in the pulmonary vascular bed at various loads

*Dexter* How high did Visscher s pulmonary venous pressure rise?

*Cournand* He must have gotten a level of 20 25 mm of mercury I am referring to the relative pressure rise of the pulmonary vein and pulmonary artery

*Dexter* In this regard the gradient of pressure between the pulmonary artery and pulmonary capillaries remains within normal limits until the pulmonary capillary pressure approaches or exceeds about 25 mm Hg Above that point the pulmonary artery pressure the gradient of pressure between pulmonary artery and capillaries and the pulmonary arteriolar resistance rise precipitously We have never found any exception to this and it appears that the arterioles at least in man constrict in response to an elevation of pressure in the capillaries above oncotic

*Stead* How do you differentiate between active constriction and increased resistance from edema formation?

*Dexter* What I meant to say was arteriolar resistance not constriction

*Stead* I would like to philosophize for Dr Shorr One may say that the initial disturbance in congestive failure is a decrease in cardiac output There is a perfectly uniform decrease in blood flow to all organs throughout the body You can say that in the

kidneys vasoconstrictor substances are formed when the blood flow is decreased and you may postulate that the renal vessels react more actively than those of other organs to such circulating vasoconstrictor substances Therefore the blood flow to the kid ney is now decreased by two factors (1) fall in cardiac output (2) active vasoconstriction out of proportion to that present in other organs

*Kety* The teleology of the phenomenon is rendered rather obscure in that the cerebral blood flow falls in a manner parallel to that of the splanchnic circulation With due respect to Stanley Bradley I submit that the brain is a more immediately vital organ than the gut and if there were a redistribution of the cardiac out put I should suspect that the purpose of a generalized vasocon striction would be to preserve the cerebral blood flow You said these observations were preliminary Are they that preliminary as to admit the possibility that cerebral blood flow does not fall as much as the others?

*Stead* I would be willing to make positive statements about the kidney and the splanchnic circulation The work on the cerebral circulation has been done by Peritz Scheinberg We have not done simultaneous determination of cardiac output and cerebral blood outflow He has selected patients that would be expected to have a low cardiac output I think the figures will stand it is important enough to collect more data

*Schroeder* I think that if you asked a physiologist 15 years ago what should be studied to determine the pathogenesis of con gestive failure he would say the adrenal pituitary kidney and heart I believe that now there is evidence accumulating which is strongly suggestive that in certain types of cardiac failure par ticularly chronic there is overactivity of the adrenal cortex (as measured by the sodium concentration of sweat and by the excre tion of corticoids) and possibly overactivity of the pituitary Some experiments being done at our institution show antidiuretic hor mone in the urine in chronic congestive failure

Another point I would like to make for the record I don t know why we are avoiding the subject of renin hypertensin, VEM and VDM in chronic congestive circulatory failure Dr Shorr s question about the reason for the vasoconstriction may be very pertinent to these mechanisms

*Shorr* I wish it were possible to provide a positive answer to Dr Schroeder's question in so far as it relates to the role of VEM and VDM in the peripheral circulatory accompaniments of chronic congestive circulatory failure I can briefly tell you what our findings are to date based on the study by Dr Zweifach and myself, in conjunction with Dr Leiter's group at Montefiore (R Mokotoff D J W Escher I S Edelman J Grossman L Leiter R E Weston B W Zweifach and E Shorr *Federation Proc* 8 *112 1949*)

Blood samples were obtained from the renal and hepatic veins and the femoral artery from normal controls and patients in chronic congestive heart failure and were assayed for VEM and VDM by the rat mesoappendix test Simultaneous renal hemodynamic and renal and hepatic oxygen extraction studies were performed In all cases of congestive failure in which both an increased filtration fraction and an increased oxygen extraction ratio were demonstrated there were significant amounts of VEM in the renal vein blood These cardiacs had markedly reduced glomerular filtration rates and renal blood flows Pronounced VDM activity was found in all hepatic vein samples in the congestive failure patients In the femoral arterial blood mixtures of VEM and VDM were present some cases showing a predominance of VEM and a few a slight predominance of VDM The only factor which appeared to be basic to this phenomenon was a reduction in the oxygen tension of the blood going to these organs VEM production by the kidney of normal subjects was also achieved by having them breathe a 10% oxygen mixture which resulted in a reduction of the average oxygen tension in the kidney These are the facts In our present state of knowledge we are unable to tell you just what the relation of high concentrations of VEM within the kidney in patients with congestive heart failure mean in so far as the changes which are observed in renal hemodynamics in this condition Whether these local concentrations of VEM favor efferent arteriolar constriction and thereby increase peripheral resistance in these kidneys is at present speculative and a matter for future investigation The same uncertainty exists with regard to the possible participation of VDM (ferritin) in the antidiuretic phenomenon of congestive heart failure VDM has been found to exert profound antidiuretic effects in animals It also is present in large amounts in the blood of patients presenting antidiuretic phenomena but the exact role of VDM in these antidiuretic phenomena still remains to be established

*Fremont Smith* May I call your attention at this point to experiments I performed (Fremont Smith F Dailey, M E and Thomas G W *J Clin Investigation 6, 9 1928)* Fremont Smith F Dailey, M E *New England J Med 206, 1286 1932)* showing that in a small group of patients with edema (nephritic nephrotic cardiac or accompanying cirrhosis in the liver) failed to have a normal water diuresis in response to water drinking This was also true of patients during the stage of rising fever following intra venous typhoid vaccine or therapeutic injection of malarial organ isms In all of these conditions the delayed diuresis following water drinking was accompanied by sharp dilution of the blood plasma as measured by chlorides sodium freezing point depression spe cific gravity total proteins and total solids while normally, water drinking results in almost no change in blood composition These patients with edema or with a rising fever therefore behaved as normal individuals would if they had been given an injection of pitressin followed by water drinking It is evident therefore that the edema in these cases was determined by a renal mechanism i e a failure of the kidney to respond to water drinking with an adequate water diuresis

*Anderson* The typhoid vaccine injection appears to disturb the temperature regulating mechanism which is centered in the hypothalamus Could it be that the vaccine injection upsets the normal mechanism of the osmoreceptors in the supraoptic nucleus as well so that water excretion is disturbed?

*Fremont Smith* Might one not say along with what you are saying Dr Anderson that it is as if the normal suppression of the antidiuretic hormone which takes place when you drink water fails and that the antidiuretic hormone therefore continues to operate thus leading to edema because of excessive tubular re-absorption or rather to a continued high level of tubular reabsorption which prevents diuresis?

*Cournand* With respect to Dr Anderson s remark it should be noted that Dr W H Hamilton several years ago suggested such a mechanism with regard to the retention of water in con gestive failure It is however, very important to know what is the horse and what is the cart

# RELATION OF CARDIAC OUTPUT TO PERIPHERAL VASCULAR ADJUSTMENT*

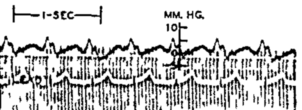
ANDRE COUPNAND
*Department of Medicine College of Physicians and Surgeons Columbia University*

With some reluctance I have accepted to talk on the subject assigned to me The main point of my presentation will be to attempt to demonstrate that although variations in the systemic circulation have some effect upon the cardiac output intracardiac dynamics are none the less the predominant factors in altering the output of the heart With this in mind it becomes impossible to ignore the role of the pulmonary venous return to the left heart and therefore to remain silent on the question of filling and emptying of the left ventricle After yesterday's Conference I felt that the presentation of data would be welcomed The paradox of the situation is worth noting that for once the medical investigator will be the one to provide factual information

The first slide (Figure 32) to be presented is concerned chiefly with some aspects of intracardiac mechanics and provides some background for future reference In Figure 32 are shown two pressure tracings taken within a few seconds in the right auricle and in the left auricle using the catheter technique (2) The scale is the same for both tracings You are familiar with the cyclic variations in the right auricle I call your attention to the drop of pressure during ventricular isometric contraction and ejection which immediately suggests that the contraction of the right ventricle plays a role in the filling of the right auricle and therefore affects blood flow in the venous system Moving over to the left auricular tracing one is immediately struck by the greater rise of pressure during auricular systole and the greater drop during early ventricular systole The latter suggests that as a result of left ventricular isometric contraction and ejection the marked pressure decrease in the left auricle favors blood motion in the pulmonary veins Also at the time of opening of the mitral valve there is a

* Aided by a grant from Commonwealth Fund
Cardio Pulmonary Laboratory Columbia University Division Bellevue Hospital

INTERAURICULAR SEPTAL DEFECT



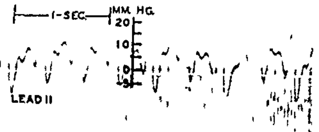




FIGURE 32

marked pressure drop in the left auricle which suggests that at the end of isometric relaxation in the left ventricle a differential pressure favors the movement of blood from the left auricle to the left ventricle All this is not said to have Dr Katz on my side Yet I believe and he will agree with me that the heart is both a suction pump and a pressure pump I leave to semantics the worries of giving a correct definition to the word suction In summary the filling of the auricles is correlated to ventricular contraction and in pari passu ejection is related intimately to cardiac filling With this in mind we can now start the discussion of our principle topic the role of peripheral circulation upon cardiac output

*Schroeder* How do you get into the left auricle?

*Cournand* This was a child of 8 months of age with an interauricular communication and no significant dilatation of any chamber of the heart We are not certain of the nature of the auricular defect The volume of shunt was calculated as very small

*Schroeder* Is it possible that the flow and pressure in the right was influenced by the patent ductus?

*Cournand* I am glad you bring that question up When I sent these tracings to Dr Carl Wiggers he suggested also that the large pressure rise in the left auricle at the time of auricular systole might be influenced by a right auricular systole occurring shortly ahead This would result in a summation of the effects of both auricular systoles Although not denying this possibility I have because of the magnitude of the cyclic variations held strongly in favor of the concept that the volume pressure relation ships in both auricles are different—the left auricle being le s distensible than the right Physiologists apart from Yandell Henderson early this century have paid little attention to the possibility that the volume pressure relationships might be dif ferent in the right and left auricles

*Dexter* What was the amount of shunt?

*Cournand* Aproximately 1/15 of the total systemic flow

*Katz* This is not peculiar to the shunt You recall in Detroit Opdyke verified in the dog what you indicated concerning the relationship of the left and right auricles in man

BLOOD VOLUME C.C./SQ.M
3000
2500
2000
1500
1000
500
0
20
40
60
80
100
120
MEAN ARTERIAL PRESSURE MM. HG
BLOOD VOLUME C.C./SQ M
3500
3000
2500
2000
500
1000
500
0
1
2
3
4
5
CARDIAC INDEX LITERS/MIN./SQ M

FIGURE 33

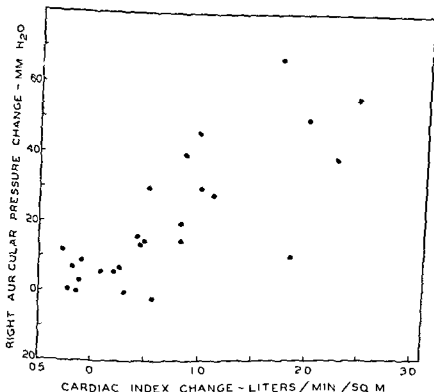



FIGURE 34

*Cournand* Dr Opdyke also found that in most dogs without septal defects the left atrial pressure is higher than the right He has failed to indicate that we were the first to suggest a difference between the distensibility curves of the left atrium and the right He also has voiced privately the opinion that the curves published in man are not comparable to those taken in dogs

Embarking now on my subject I shall first discuss the relationship between venous return and cardiac output then the relationship between pressure variations in the arterial system and the cardiac output and finally broach on the problem of the pulmonary circulation and cardiac output In an artificial way the responses of the right and left heart are considered separately when of necessity they are closely related As we progressed in our studies we became firmly convinced that the left ventricle is the key to the circulation And yet the law of the heart has

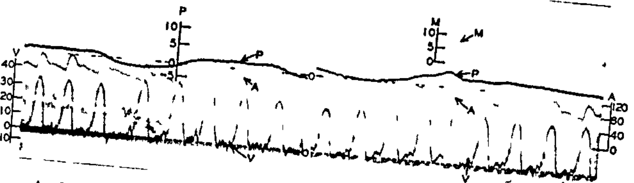

AMBIENT BREATHING
AS
IPP BREATHING TYPE I CURVE
P
10
5
0
-5
M
10
5
0
M
P
A
V
40
30
20
10
0
10
0
A
120
80
40
0
A = BRACHIAL ARTERY V = RIGHT VENTRICLE P-PLEURA M = MASK ECG = LEAD II
ALL PRESSURES IN MM HG

FIGURE 35

only been studied for the right ventricle the left ventricle until recently remaining in the shadow

In 1942 due to the urgency of the problem we became interested in the question of the dynamics of the circulation in shock (3 4 16 17) It became immediately apparent that under those conditions there is a definite correlation between venous return and cardiac output As seen in Figure 33 it is obvious that the mean arterial pressure is not well correlated with the blood volume in patients with severe skeletal traumas or external hemorrhage in shock There is however a good correlation between the blood volume and the cardiac index

In Figure 34 it is apparent that there is a definite correlation between the rise in cardiac output and the rise in right atrial pressure in the same individuals studied before and after treatment

Further evidence concerning the relationships between venous return and cardiac output may be adduced from more recent studies In 1945 we were asked by the Air Corps to study the effect of positive pressure breathing upon the dynamics of the circulation (5 11 13 14 15) By that time we had substituted the Hamilton manometer for the saline manometer and were measuring pressure in the right ventricle rather than right atrial pressure With Hurley Motley and Lars Werko we studied different types of pressure breathing devices and in few patients with a therapeutic pneumothorax we recorded intrapleural pressures simultaneously with intraventricular pressures We then were able to calculate the net filling pressure of the right ventricle (net end diastolic pressure) and to correlate this measurement with the cardiac output In Figure 35 are shown the pressure recordings in such a study and in Figure 36 are shown the data calculated from these tracings during ambient air breathing and pressure breathing You will note the phasic change in intrapleural pressures and in net filling pressures in the right ventricle You will note also that the duration of the cardiac cycle is recorded at the bottom of the Figure The factor of cardiac rate would appear to influence the filling pressure adversely the slower the rate the smaller the filling pressure By integrating both filling pressure curves before and during pressure breathing it was found in this particular experiment that a decrease in filling pressure of the order of 2 mm Hg corresponded to 40% decrease in cardiac output This observation like others made in this study indicates

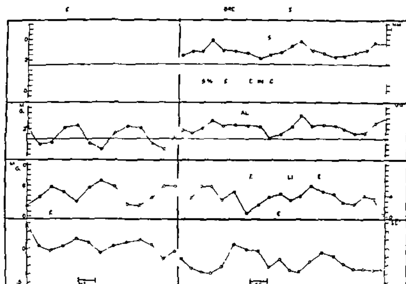


FIGURE 36

that small pressure variations in the right auricle may correspond to large variations in cardiac output In general it is not appreciated first that the right mean auricular pressure does not correspond to the filling pressure of the right ventricle and second that a 2 mm Hg change is a significant change for the right auricle and ventricle in diastole This statement is of considerable interest in view of what has been previously stated namely that the right auricle is much more distensible than the left and that the volume pressure curves in the right auricle show at low pressure large volume changes for small pressure changes (12)

*Stead* What about the change in the peripheral resistance?

*Cournand* I am dealing strictly with the right heart You mean the pulmonary vascular resistance?

*Stead* I wonder if the change may not be comparable to that seen on opening an AV fistula? I think you have omitted one variable I assume that when the pulmonary artery is connected up with the vein the output of the right ventricle would increase just as the output of the left ventricle increases

*Cournand* Dr Stead is raising a question which deals with the pulmonary circulation Let us consider what would happen if

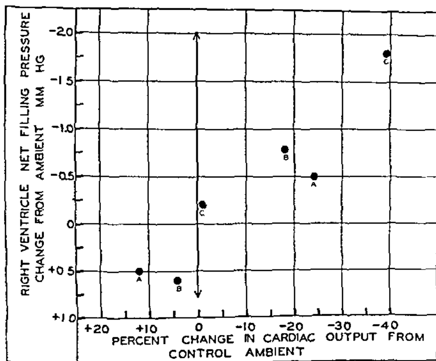



FIGURE 37

a pulmonary arteriovenous fistula or some like mechanisms occurred under the conditions of our experiments It should be mentioned first that the pressure decrease from the pulmonary artery to the left auricle is of the order of 4 to 6 mm Hg There fore the opening of an AV fistula could not have a striking effect on the total pulmonary vascular resistance unless it was very large I will therefore not deny that it might have some effect on the emptying of the right ventricle

In Figure 37 are plotted all the data obtained in this and a few similar studies concerning the relation which exists between changes of net end diastolic pressure in the right ventricle and changes of cardiac output There is as can be seen a remarkable correlation Unfortunately the number of observations are not too large

I would like to turn now to the problem of the effect upon the venous return of closing and opening an arteriovenous fistula in the systemic circulation Dr Stead has studied a large number of patients with an AV fistula measuring the variations in cardiac output with the Ballistocardiograph He showed that closing the fistula reduced the impacts and presumably the stroke volume In some studies with the cardiac catheterization technique he was unable to establish a relationship between the cardiac output variations and the right auricular pressure variations The two next cases will I believe demonstrate that this may not always be correct (1)

In Table XIV are tabulated some data obtained in a man of 70 years of age before and after closure of a very large AV fistula in the groin The heart of this elderly gentleman appeared normal Yet when the aneurysm was closed manually end diastolic pressure in the right ventricle dropped from 10 to 1 mm Hg while the mean auricular pressure dropped from +1 to -2 mm Hg The *cardiac output markedly decreased while the heart rate changed* little It would then appear that the reduction in filling pressure of the right ventricle was related to the reduction in output It is not my intention to deny that the increase in peripheral resistance was influential in reducing the stroke volume of the left heart

*Stead* How was the fistula occluded?

*Cournand* The fistula was occluded by local compression

TABLE XIV

HEMODYNAMIC CHANGES IN A FEMORAL ARTERIO VENOUS ANEURYSM WITH THE ANEURYSM PATENT AND OCCLUDED

| #408 Male Age 70 | *Aneurysm* Patent | *Aneurysm* Occluded |
|---|---|---|
| Rt Ventricular Pressure S/D mm Hg | 41/10 | 33/1 |
| Rt Auricular Pressure Mean mm Hg | 1 | −2 |
| Cardiac Index L/min/m² BSA | 8 46 | 3 99 |
| Heart Rate beats/min | 75 | 71 |

TABLE XV

HEMODYNAMIC CHANGES IN A FEMORAL ARTERIO VENOUS ANEURYSM WITH THE ANEURYSM PATENT AND OCCLUDED

| #395 Male Age 62 | Aneurysm Patent | Aneurysm Occluded |
|---|---|---|
| Brachial Artery Pressure S/D mm Hg | 116/57 | 158/87 |
| Brachial Artery Pressure Mean mm Hg | 75 | 105 |
| Rt Ventricular Pressure S/D mm Hg | 51/11 | 47/5 |
| Rt Auricular Pressure Mean mm Hg | 4 | 0 |
| Cardiac Index L/min/m² BSA | 4 05 | 2 79 |
| Heart Rate beats/min | 8[illegible] | 55 |

*Lamport* Were results obtained immediately after compression or at equilibrium?

*Cournand* The data were obtained approximately 10 minutes after beginning of compression

The second case illustrated in Table XV was that of an elderly male who had been previously in cardiac failure but was compensated at the time of the study The changes are comparable to the previous case and you will note also that the drop in right atrial pressure after occlusion is approximately 4 mm Hg

*Katz* Dr Cournand in that last slide would you like to attack the potential question that Dr Stead might ask by pointing out that the resistance on the right side went down while the resistance on the left side went up with occlusion so that the resistance would be different on the two sides?

*Cournand* The question can be answered very simply I don t have the data to calculate pulmonary vascular resistance in this case because the mean pressure in the pulmonary artery was not




FIGURE 38

measured or the pressure in the left auricle Perhaps Dr Dexter may be able to give us an answer to this question in the near future

*Stead* It is worth pointing out that the age of the people certainly modifies the results obtained In a group of young people with AV fistulas of comparable size some even larger there was no change at all in ventricular pressure in the systolic or diastolic or in the pulmonary arterial pressures while the fistula was open and shut

*Cournand* After what length of time?

*Stead* Periods of roughly five minutes We were not able to make any more sense out of the atrial pressures when they were recorded with the Hamilton manometer We simply never found any consistent change with the fistula providing care is taken to prevent pooling of the blood when the fistula is occluded

*Cournand* Are you satisfied that the end diastolic pressure was measured accurately?

*Stead* I would say taking the group as a whole that they seemed to be satisfactory

*Cournand* Figure 38 shows what happened when the pressure over the AV fistula was released There was a striking change in the form of the pressure tracing in the brachial artery Dr Wiggers would probably suggest that these tracings indicate a high velocity during ejection

I shall turn now to some data obtained in two cases of Wolf Parkinson White syndrome studied by Dr Ferrer Harvey et al during and after an attack of nodal tachycardia (8) In both cases illustrated in Table XVI the mean right atrial pressure was significantly elevated during the period of nodal tachycardia and returned to normal after the W P W rhythm was resumed with out any change in cardiac output and peripheral resistance Unfortunately we were unable to record the right ventricular end diastolic pressure during the period of tachycardia as the nodal rhythm instantly ceased after one premature contraction when the tip of the catheter was inserted into the right ventricle Figure 39 illustrates the pressure records taken during the period of nodal tachycardia in the right auricle in the superior vena cava

TABLE XVI

HEMODYNAMIC STUDIES IN TWO PATIENTS WITH WOLFF PARKINSON WHITE SYNDROME AND NODAL TACHYCARDIA

| PATIENT | PULSE RATE beats/min | BLOOD PRESSURES in mm Hg Brachial Artery Syst/Diast | Brachial Artery Mean | Rt Vent Syst/Diast | Rt Atrium Mean | CARDIAC OUTPUT L/min/m² | cc per beat | PERIPHERAL RESISTANCE dynes cm $^{-5}$ sec |
|---|---|---|---|---|---|---|---|---|
| Normal | | 120/70 | 85 | 30/2 | 3 to −3 | 3 12 ± 0 1 | 50 90 | 1500 |
| G F | | | | | | | | |
| Nodal tachycardia | 187 | 102/73 | 80 | | +7 8 | 3 39 | 27 | 1130 |
| W P W conduction with right bundle of Kent | 78 | 101/66 | 77 | 28/3 | +1 5 | 3 16 | 60 | 1240 |
| K N | | | | | | | | |
| Nodal tachycardia | 178 | 105/77 | 90 | | +5 8 | 2 30 | 24 | 1600 |
| W P W conduction with left bundle of Kent | 121 | 101/72 | 84 | 32/1 | +0 5 | 2 29 | 34 | 1590 |


NODAL TACHYCARDIA
B A
RT AT
INTRACARDIAC LD
20
10
B A
120
80
60
SUP VENA CAVA
INTRACARDIAC LD
B A
SUBCLAV V
INTRACARDIAC LD

FIGURE 39

and in the subclavian vein, beyond the first venous valve The intracardiac E C G lead is also recorded This shows clearly that the peak of the pressure rise of large magnitude observed in the right auricle and the superior vena cava takes place after the QRS complex Tricuspid regurgitation is strongly suggested by this tracing You will note also, and these observations have some bearing upon some points discussed by Dr Bazett yesterday that beyond the first venous valve the wave of large magnitude disappears and is replaced by a small notch It is obvious that retrograde flow does take place in the large veins during part of the cycle and that the mean pressure in the right auricle is in no way related to the filling pressure of the right ventricle Briefly then in individuals with nodal tachycardia and/or tricuspid insufficiency mean central venous pressure and its variations are not correlated with cardiac output changes

Returning to the studies of shock I wish to introduce peripheral vascular resistance as a factor influencing the cardiac output In studies on the effects of treatment with whole blood with concentrated albumin and saline, and with gelatin, we were greatly impressed by the great variations in calculated peripheral vascular resistance following treatment In Table XVII data concerning the total blood volume hematocrit mean blood pressure mean right atrial pressure cardiac output and calculated peripheral vascular resistance have been tabulated in two groups of patients before and after treatment with whole blood and with concentrated albumin (6) The contrast between both treatments is striking The cardiac output rose much more following the infusion of concentrated albumin in saline than following whole blood transfusion The chief factor involved in this disparity of hemodynamic response in these two series of cases the state of circulation of which was approximately comparable before treatment appears to be the marked reduction in the hematocrit in the second group The factor of blood viscosity or plasticity as Dr Lamport prefers to call it must then be taken into account in any consideration of the factors influencing peripheral vascular resistance With several specimens of degraded gelatin the increase in peripheral vascular resistance was very striking In a few cases of shock treated with this blood substitute the mean arterial pressure rose very significantly while the cardiac output remained at the initial low level

TABLE XVII

COMPARISON OF THE HEMODYNAMIC CHANGES IN TWO GROUPS OF PATIENTS IN SHOCK (TRAUMA EXTERNAL HEMORRHAGE) TREATED WITH (I) WHOLE BLOOD AND (II) CONCENTRATED ALBUMIN AND SALINE

| | State | Blood Volume per m² B S Total cc | Blood Volume per m² B S Het % | Arterial Mean Pressure mm Hg | Right Atrium Pressure mm H O | Cardiac *Output* L/min/m² | Peripheral* Resistance per m² B S |
|---|---|---|---|---|---|---|---|
| GROUP I Blood treated | | | | | | | |
| No of cases 19 | Before | 1807 | 34 | 49 | +10 | 2 11 | 2001 |
| Average transfusion = 910 cc | | | | | | | |
| Average saline infusion = 709 cc | After | 2248 | 35 | 79 | +36 | 3 21 | 2059 |
| GROUP II Albumin treated | | | | | | | |
| No of cases 7 | Before | 2007 | 36 | 65 | + 4 | 2 34 | 2185 |
| Average concentrated albumin injected = 53 5 gm | | | | | | | |
| Average saline infusion = 702 cc | After | 2271 | 28 | 76 | +33 | 4 14 | 1458 |

*dynes cm 5 sec × m² B S

In our studies of shock before treatment we were impressed as Dr Carl Wiggers had been previously that the cardiac output was low despite the maintenance of peripheral vascular resistance within normal limits This was true of all non alcoholic individuals Apparently up to a certain limit the reduction in stroke volume sets up some reflex mechanism the result of which tends to decrease the size of the arteriolar lumina proportionally to the reduction in blood flow In alcoholic individuals—and there were many at Bellevue—following traumatic shock the mean arterial pressure relative to the decrease in cardiac output was much lower than in non alcoholic individuals Vasodilatation was an important factor even in reversible cases of shock I shall not argue whether the liver function was involved except to state that autopsies performed on some of these cases failed to reveal, as a rule cirrhosis of the liver or fatty degeneration That some humoral factor (VDM) might explain this phenomenon is not altogether impossible although the role of ethyl alcohol on the nervous centers in particular the vasomotor centers cannot be excluded

*Katz* In that regard while it may be argued that the change in venous pressure correlated with cardiac output our results recently were the contrary In a series of dogs with hypothermia and hyperthermia we observed marked changes in cardiac output although the venous pressure remained unchanged [Prec O Rosenman R, Braun K Harris P Rodbard S and Katz L N *J Clin Investigation* 28 *293 (1949)*]

*Cournand* The following case illustrates well the influence of blood transfusion in a subject in profound shock (6) The patient, a business executive was celebrating Christmas with other members of his staff While dancing with a young employee he backed into an elevator shaft the door of which was open Both fell down five flights The girl died and the patient was transported to Bellevue Hospital in profound shock and 13 compound fractures In Figure 40 are shown diagrammatically the various measurements of the circulation before during and after very large blood transfusions The peripheral vascular resistance at first somewhat elevated dropped significantly and returned progressively to a normal value after treatment and after the effects of mild alcoholism were dissipated Meanwhile atrial pressure and cardiac output rose very markedly under the influence of blood replacement The patient ultimately survived

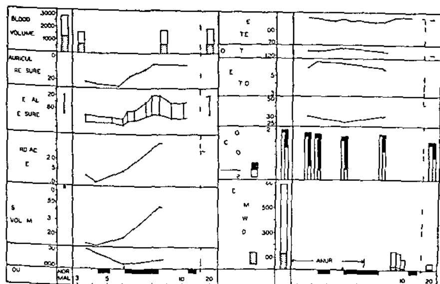



FIGURE 40

*Lamport* At these low pressure levels I think you encounter the pseudoplasticity of blood as an important factor When the blood pressure is low resistance becomes a poor index of hindrance and tends to exaggerate its size In other words I would say the hindrance was subnormal before treatment and probably remained low after therapy rather than dropping from fairly normal levels

*Cournand* How can one analyze data where the hematocrit and the mean arterial pressure were measured making allowance for blood plasticity in calculating peripheral vascular resistance?

*Lamport* Very approximately I have used a simple straight line that does not pass through zero In other words I have subtracted 20 mm yield pressure from the blood pressure in order to compensate for this factor

With respect to the viscosity and the change in hematocrit which you referred to I published a paper on the kidney which had charts in it by which one can make approximate allowances for change in hematocrit and in plasma protein concentration Such data can thus be utilized in order to obtain an approximation of the hindrance which I think would be preferable to resistance

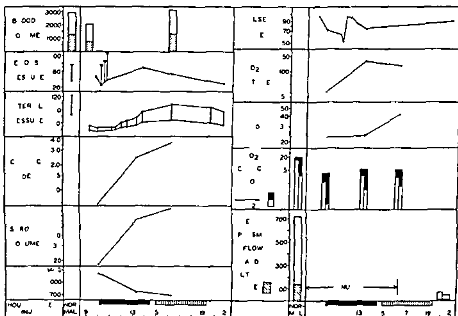



FIGURE 41

as a measure of vascular tone (See Lamport presentation references 13 15 p 131)

*Cournand* The next case (6), illustrated in Figure 41 brings again to the fore the unusual relations between peripheral vascular resistance and cardiac output during recovery from shock In addition it shows the impossibility of interpreting data on auricular pressure in conditions where the intrapleural pressure does not remain normal This patient with a bullet wound of no serious consequence had been exposed to severe cold outdoors several hours On admission his body temperature was 26 C The cardiac output was extremely low but the right auricular pressure was only slightly reduced to approximately 30 mm H O The very rigid chest due to intense cold and body refrigeration suggests that intrathoracic pressure conditions were far from normal and therefore the measured mean atrial pressure bears little relation to the actual net filling pressure As part of the treatment the patient was warmed and received large transfusions of whole blood Following these the cardiac output rose considerably returning within a few hours to normal while the peripheral resistance dropped considerably Talbot in his studies of individuals

with carcinoma treated by refrigeration has called attention to the considerable degree of vasodilatation taking place during the warming up period following treatment In one case it seems probable that vasodilatation favored the great increase in cardiac output, although it is not altogether impossible that a rise in cardiac output due to blood replacement and an increase in venous return through a reflex mechanism (aortic body) might have favored vasodilatation The complexity of mechanisms involved in circulatory readjustments in such cases and the difficulties of an exact interpretation are quite evident

I shall now displace the center of focus to the left ventricle and consider at first the effects of a sustained increase in systemic vascular resistance upon the output of the heart in uncomplicated essential hypertension With Dr Goldring and Dr Chasis and some of their associates, we studied a few years ago five cases of malignant hypertension before and after sympathectomy The measurements of the circulation are illustrated in Table XVIII As you will note the cardiac output was within normal limits and remained unchanged although the mean arterial pressure decreased significantly

*Grimson* Was it a complete sympathectomy including stellate and upper dorsal ganglia or a splanchnicectomy leaving the stellate ganglia and cardiac accelerators intact?

*Goldring* It was a bilateral sympathectomy from the 8th dorsal to second lumbar

*Cournand* With Drs Ferrer Harvey and Cathcart we have since studied other similar cases (Table XIX) As long as symptoms of left ventricular failure are not present the cardiac output remains normal and the mean pulmonary arterial pressure does not rise However if hypertension is associated with arteriosclerotic changes in the coronary arteries the state of the circulation changes greatly All the cases illustrated in Table XX were known hypertensives with evidence of arteriosclerotic heart disease but without clinical manifestations of left ventricular failure The cardiac output is low but the end diastolic pressure in the right ventricle is normal and so are the pressures in the pulmonary artery

*Schroeder* There is only one case that you could call hypertensive by definition with a diastolic elevation

## TABLE XVIII

**EFFECT OF BILATERAL SYMPATHECTOMY UPON CARDIAC OUTPUT AND PERIPHERAL RESISTANCE IN FIVE CASES OF ESSENTIAL HYPERTENSION**

| | Body Surface Area m² | Mean Arterial Blood Pressure mm Hg | Cardiac Output | | | Peripheral Resistance dynes cm⁻⁵ sec | AV Difference cc/L | O2 Intake cc/min/m² | Pulse Rate beats/min |
|---|---|---|---|---|---|---|---|---|---|
| | | | L/min | L/min/m² | cc per beat | | | | |
| Average before operation | 1 68 | 160 | 5 70 | 3 39 | 70 | 2250 | 41 | 138 | 82 |
| Average after operation | 1 60 | 135 | 5 52 | 3 15 | 64 | 1960 | 38 | 131 | 87 |

## TABLE XIX

### HEMODYNAMIC DATA IN FIVE PATIENTS WITH HYPERTENSIVE CARDIOVASCULAR DISEASE, ENLARGED HEARTS AND NORMAL SINUS RHYTHM

| Case | CI | $O_2$ cons | Pressures in mm Hg | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | | BA | | PA | | RV |
| | L/m /m² | /min/m² | S/D | M | S/D | M | E d D |
| 399 | 3.37 | 119 | 206/108 | 147 | | - | 3 |
| ‡391 | 3.87 | 135 | 158/91 | 119 | 21/ | | 3 |
| ‡390 | 2.79 | 157 | 210/130 | 170 | 23/ | | 4 |
| 513 | 2.59 | 116 | 183/98 | 128 | 18/6 | 11 | 3 |
| ‡509 | 4.32 | 151 | 241/113 | 156 | 18/8 | 13 | 3 |

## TABLE XX

### HEMODYNAMIC DATA IN FOUR PATIENTS WITH ARTERIOSCLEROTIC AND HYPERTENSIVE HEART DISEASE AND ENLARGED HEARTS

| Case | CI | $O_2$ cons | Pressures in mm Hg | | | | | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | BA | | PA | | RV | |
| | L/m /m² | /m /m² | S/D | M | S/D | M | End D | |
| ‡402 | 2.06 | 144 | 180/75 | 107 | 24/ | | 3 | AF LBBB |
| ‡506 | 1.94 | 101 | 116/8[illegible] | 98 | 18/11 | 13 | 4 | NSR Recent Infarct |
| ‡482 | 2.73 | 129 | 116/66 | 88 | 18/10 | 12 | 0 | NSR LBBB |
| ‡429 | 1.83 | 101 | 162/100 | 126 | | | 1 | NSR |

*Cournand* All these cases have been followed for long periods in the hypertension clinic

*Schroeder* They have been sympathectomized?

*Cournand* No

*Schroeder* They have recovered spontaneously?

*Cournand* They were known hypertensives with arteriosclerotic heart disease whose blood pressures dropped to lower levels This is not unusual

The striking change here appears to be a low cardiac output In all but one there were rhythm disturbances and I should like to stress that frequently in the presence of rhythm disturbances the cardiac output is greatly reduced

*Katz* May I ask you to indicate whether the arrhythmias were sinus tachycardia or ectopic rhythm?

*Cournand* Ectopic rhythm or conduction defects

With Drs Harvey Ferrer et al we studied a number of cases with left ventricular failure before and during acute digitalization (10) They were in the early stages of left ventricular failure In order to appraise correctly the significance of hemodynamic changes following digitalization it was essential to run a control series During an 18 month period twenty patients were studied under precisely the same conditions as the subjects with mild left ventricular failure Pressure recordings and cardiac output measurements were repeated at various intervals of time The statistics appear in Tables XXI and XXII The changes in oxygen consumption oxygen AV differences and calculated cardiac

TABLE XXI

ANALYSIS OF DIFFERENCES BETWEEN TWO SUCCESSIVE MEASUREMENTS OF CARDIAC OUTPUT IN 20 CONTROL PATIENTS NOT RECEIVING MEDICATION

| | Mean Difference | Range |
|---|---|---|
| Cardiac output in % of first determination | 4 8 | −9 0 to +9 2 |
| Oxygen consumption in cc /min /m² B S | 7 0 | −18 to +12 |
| Arteriovenous difference in volume % | 0 2 | −0 3 to +0 5 |
| Heart rate in beats per minute | 2 0 | −6 to +4 |

TABLE XXII

STATISTICS OF TWO SUCCESSIVE DETERMINATIONS OF CARDIAC OUTPUT IN 20 CONTROL PATIENTS NOT RECEIVING MEDICATION

| | First Determination | | | Second Determination | | |
|---|---|---|---|---|---|---|
| | Mean | S E | Range | Mean | S E | Range |
| Oxygen consumption—cc /min /m | 140 | ±2 6 | 158 10 | 137 | ±2 3 | 156 119 |
| Cardiac index—L/min /m | 3 46 | ± 19 | 5 01 2 03 | 3 42 | ± 19 | 5 19 2 02 |
| AV difference—volume % | 4 3 | ± 23 | 6 8 3 0 | 4 3 | ± 26 | 7 0 2 8 |
| Pulse rate—beats/min | 77 | ± 35 | 117 54 | 76 | ± 35 | 117 52 |

Average time between two successive determinations = 27 minutes (range 11 60)

Average time between beginning of study and second determination = 148 minutes (range 48 186)

output are small A good knowledge of the patients and a well trained team are indispensable to obtain this kind of data With emphasis I insist that a stable state of basal metabolism can be reached with the direct Fick method and that opinions to the contrary suggest to my mind prejudice or poor technique

*Lamport* In the individual cases how good were the comparisons between the first and the second determinations?

*Cournand* The mean difference in cardiac output was 4 8% with a range of −9 to +9% while the range of variations in oxygen consumption was from −18 to +12 cc /min /m² of body surface

In Figure 42 are illustrated the findings in one case of left ventricular failure associated with hypertensive cardiovascular disease As in all the other cases similarly studied the pulmonary function was found not to be altered

Before digitalization the cardiac output and stroke volume were considerably reduced the pulmonary arterial pressures strikingly elevated the right ventricle and diastolic pressure low normal Following acute digitalization cardiac output and stroke

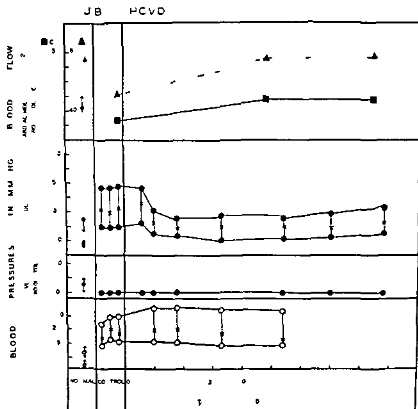



FIGURE 42

volume increased significantly the pulmonary arterial pressures returned to approximately normal the right ventricle end diastolic pressure remained unchanged while the pulse pressure in the systemic arteries increased markedly

*Katz* Digoxin?

*Cournand* About 1 to 1 5 mg of digoxin depending upon the weight was slowly injected intravenously, diluted in 20 cc saline We assumed that the rise in pulmonary arterial pressure reflected an increase in pulmonary venous and left auricular pres sures With better emptying of the left ventricle following the action of digoxin on the myocardium the pulmonary venous pres sure decreased and pari passu the pulmonary artery mean pres sure returned to normal (Two other slides were shown illustrat

ing the same changes in two patients in left ventricular failure one with hypertensive and arteriosclerotic heart disease and one with rheumatic heart disease)

*Kety* What happened to the right auricular pressure?

*Cournand* We do not measure it as a rule In these studies we employ a double lumen catheter one distal lumen opening in the pulmonary artery and the other in the outflow tract of the right ventricle Once in position no further upsetting manoeuvres take place The effect of the venous return to the right heart is measured in the right ventricle at the end of diastole In all of these cases the end diastolic pressures were normal and did not change significantly

In relation to the problem of the effects of a change in peripheral vascular resistance upon the cardiac output the next figure (Figure 43) is of great interest Drs Ferrer Harvey et al (9) have shown that quinidine has a definite vasodilator effect in man Dr Hyatt has recently shown the same effect in animals In a case of left ventricular failure treated conventionally with digitalis and illustrated here the oral administration of 0 8 gm quinidine caused a striking decrease in pulmonary arterial pressure an increase in cardiac output and a considerable fall in systolic and pulse pressures in the brachial artery The following sequence of events might be postulated first a decrease in peripheral vascular resistance second a better emptying of the left ventricle reduction in residual blood volume and in filling pressure and third a reduction in pressure in the pulmonary venous system which was reflected in a drop in the pulmonary artery

*Katz* After how long did that effect take place?

*Cournand* After one to one and a half hours

*Grollman* Did the patients have arrhythmias?

*Cournand* No

*Schroeder* I believe this is a common effect of the quinidine group

*Cournand* Dr Hyatt from North Carolina studied drugs of this group He welcomed our findings because there was some question whether in his experiences the effect was not due to a decrease in cardiac output which he had not measured Analysis

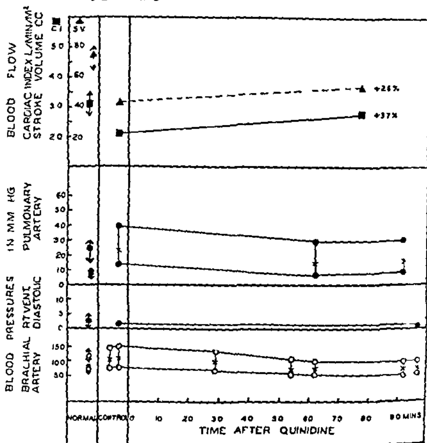



FIGURE 43

of the interrelated effects between changes in peripheral vascular resistance and changes in cardiac output is always complex especially in view of the fact that digoxin might have a direct vasoconstrictor effect

*Katz* In the dog this is true

*Cournand* In two subjects with normal hearts plotted in Figure 44 as open circles, this would appear to be true also If you compare the changes in cardiac output and mean arterial blood pressure following the intravenous injection of digoxin a striking rise in peripheral resistance is apparent which in these cases is associated with a drop in cardiac output Whether the

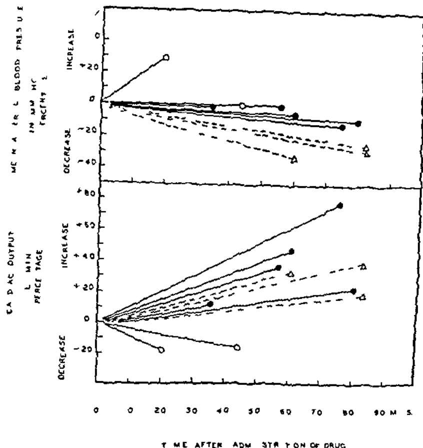



FIGURE 44

drug bv its action on the normal myocardium causes a reduction in output which in turn in a reflex manner (aortic body) causes vasoconstriction or whether digoxin causes vasoconstriction followed by a reduction in left ventricular output cannot be decided from our data The latter mechanism would appear more likely In the group of patients in left ventricular failure treated with quinidine (drawn as open triangles in Figure 41) the decrease in peripheral vascular resistance is considerable The magnitude of this decrease contrasts with the small reduction seen in patients in left ventricular failure treated with digoxin (shown as closed circles) in whom the mean brachial artery pressure change is very

small the cardiac output rise is as a rule somewhat larger This might be looked upon as a confusing situation unless explained as follows namely that in digoxin treated cases the primary action is on the myocardium of the left ventricle causing a marked increase in output the final level of systemic blood pressures results form the opposing effects of vasodilatation caused by the reflex action on the aortic body of an increased stroke volume and vasoconstriction due to direct action of digoxin on peripheral vessels Interpretation of pressure variations in relation to cardiac output variations is always very difficult especially if the injected drug has *per se* a distinct peripheral action

In order to escape these difficulties I shall now in the remainder of my presentation discuss some relations existing between cardiac output and pulmonary circulation

Nature often presents us with interesting situations, the like of which physiologists have often great difficulties in simulating In Figure 45 appear three tracings taken almost simultaneously in the left ventricle the right ventricle and the pulmonary artery of a young child with an interventricular septal defect This defect in so far as the left ventricle is concerned is the equivalent of an AV fistula in the systemic circulation You will note that both ventricles have maintained their hemodynamic individuality The systolic and end diastolic pressures in the left ventricle are much higher than corresponding values in the right ventricle You will note also that in spite of an increase in pulmonary blood flow *the pressures in the pulmonary arteries are nearly normal* Because the left ventricular flow and the right ventricular flow are identical although markedly increased it is of some interest to point out the striking differences in both end diastolic pressures Hence my initial remark that it is high time to study the law of the heart for the left ventricle separately and simultaneously with the right ventricle The remark concerning the negligible pressure rise in the pulmonary artery in this case in the presence of a large blood flow may be supplemented by the statement that the pulmonary vascular resistance taking into account mean pulmonary arterial pressure and left ventricle end diastolic pressure remained low This accords well with the observations made in a series of normal individuals (18) and in subjects after pneumonectomy (7) in whom the function of the remaining lung is normal While blood flow through each lung may increase to approxi

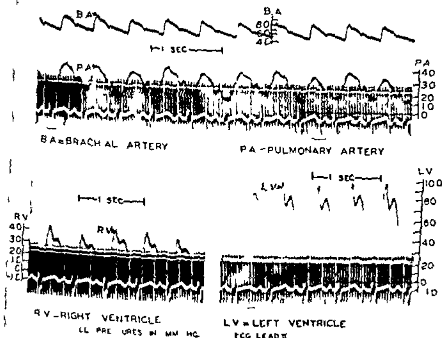



FIGURE 46

mately three times normal no pressure rise is observed in the pulmonary artery The pulmonary circulation operates at low pressures the vascular bed being very distensible If however as in cases of cor pulmonale the pulmonary vascular bed is reduced then a small rise in cardiac output may cause a significant rise in pulmonary arterial pressures This question is definitely outside the subject under discussion however some aspects of cor pulmonale are germane to our problem In Figure 46 are presented hemodynamic data in a woman with cor pulmonale before and after acute digitalization This patient presented clinical evidence of right ventricular failure substantiated by the observation of a considerable increase in right ventricle end diastolic pressure The pulmonary artery pressures were very high presumably as a result of considerable increase in resistance in the pulmonary vascular bed due to vascular lesions polycythemia and a reduced vascular bed The large cardiac output a characteristic finding in most cases of chronic cor pulmonale does probably also play a

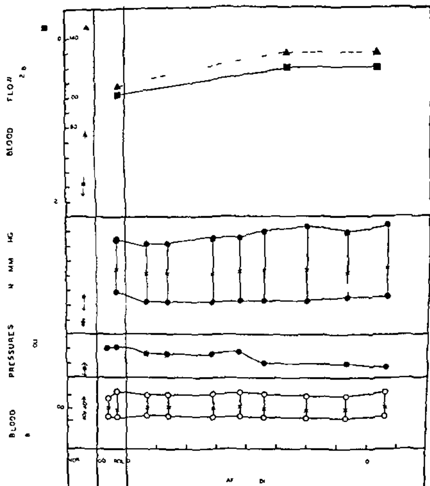



Figure 46

part in the high pressures in a pulmonary vascular bed reduced in size

Following the intravenous injection of 1 5 mg of digoxin the cardiac output rose while the right ventricle end diastolic pressure dropped very significantly With this rise in output there was a small increase in pulmonary systolic and pulse pressures as one would expect It is not necessary to contrast these results with

those previously discussed in left ventricular failure The differences in the response of both ventricles while in failure are too obvious although the action of the drug on the myocardium of the diseased ventricle is quite similar Let me point out that obviously, the left ventricle must be intact in cases of cor pulmonale in order to maintain a large blood flow

In my probably too lengthy peregrinations through the circulation during which I proceeded against the direction of blood flow I have left many stones unturned It has been the great merit of Dr Stead to call the attention of students of the circulation in man to the importance of variations of peripheral resistance in the control of cardiac output With improvements in our technique of investigation in man it has become possible to obtain a better overall view of the widespread readjustments taking place in the circulation when initially a single factor appears to operate The study of the regional redistribution of the circulation following any significant change in overall flow and pressures appears to me among the most important problems to solve in the future

In concluding I hope to have impressed you with the following

1) Both ventricles their venous reservoir and the peripheral vascular system distal to them are strikingly different dynamically Whereas the peripheral venous reservoir of the right ventricle is markedly distensible that of the left ventricle is much less so Whereas the resistance to flow in the pulmonary circulation is low that in the systemic circulation is higher

2) Ventricular filling and ventricular ejection are mutually dependent and also dependent upon the pathologic state of the myocardium

3) In the maintenance of a normal or high output the state of the left ventricle is of paramount importance

4) The mean auricular pressure is a poor index of the filling pressure in the right ventricle

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*Goldblatt* This afternoon s session will begin with a discussion by Dr Grimson of a topic of great interest to all of us the role of the sympathetic nervous system in hypertension as disclosed by a study of the action of sympatholytic and depressor drugs

# ROLE OF SYMPATHETIC NERVOUS SYSTEM IN HYPERTENSION AS REVEALED BY THE ACTION OF SYMPATHOLYTIC AND DEPRESSOR DRUGS

KEITH S GRIMSON
*Department of Surgery Duke University School of Medicine*

Today I want to deal with the role of the sympathetic nervous system in hypertension and the related role of the sympatholytic drugs There is a difference

First it might be well to review rather quickly some preparatory stages in the development of our present experience concerning hypertension It is recognized that the problem of clinical hypertension must be complex Complexity arises from the variety of factors which could cause hypertension The renal mechanism is one Some work was done in the early days with renal hypertension demonstrating that when either renal artery is clamped there is within a matter of hours some elevation of blood pressure As you know further studies were done to produce renal hypertension of a chronic sort using Goldblatt clamps before or after total sympathectomies The sympathectomy produced a slight reduction of blood pressure However when the renal arteries were clamped pressure rose Several investigators did this simultaneously Each has confirmed the conclusion that the renal mechanism will work in the absence of the entire paravertebral sympathetic ganglia and chains or the connections of the sympathetic system between the spinal cord and the peripheral ganglia and vascular bed

If one goes at the experiment a little differently and instead of eliminating the sympathetic nerves produces an overactivity of these nerves to the adrenal gland and the kidneys one has an interesting result All of the connections of the sympathetic chains except those to the adrenal glands and to the kidneys were eliminated by surgery Then an overactivity theoretically of those remaining nerves was produced by eliminating the buffer nerves of the carotid sinus heart and arch of the aorta An elevation of blood pressure occurred during the period that the kidneys were

receiving this over active sympathetic nerve supply but ceased when the nerves to the kidney along the renal arteries were divided The blood pressure then fell again The converse is not true If you denervate the kidneys alone and then divide the buffer nerves you will definitely have a neurogenic hypertension that is in no way dependent upon the nerves to the kidneys

Although our main interest is in neurogenic aspects let me say again that we are quite aware of the complicated situation and the multiplicity of factors encountered in dealing with clinical hypertension The neurohumoral mechanisms of Selye and Heimbecker *are postulated at least as not dependent upon the sympathetic* nervous system

For further orientation there is evidence that arteriolar disease might be another factor in clinical hypertension not amenable to sympathectomy of any sort medical or surgical However evidence has developed lately that there might be an indirect influence of sympathectomy produced by eliminating vasomotor activity and putting these vessels at rest in an early stage of arteriolar disease There is some evidence minimal and controversial that some arteriolar change may occur in some parts of the body early in the hypertensive disease process but there is better evidence that in a course of long sustained hypertension definite changes will occur

The concept of neurogenic hypertension theoretically applied to man is then one in which abnormal activity of the sympathetic nerves or their reflex regulation is involved but in which all of these other factors may exist or develop According to this concept of blood pressure regulation through the vasomotor centers afferent vasopressor influences originate perhaps reflexly or psychosomatically and balance against the buffering action of the depressor nerves Unless properly compensated these pressor stimuli might cause hypertension

'Neurogenic hypertension can be produced in the experimental animal as Heymans and some before him have shown This *has been done in at least 180 animals in our laboratories removing* the two carotid sinuses dividing one depressor sympathetic vagus trunk completely on one side and on the other side eliminating as best you can the depressor trunk and often the sympathetic but leaving most of this last vagus Following elimination of these

governing or buffering nerves hypertension as judged by intra arterial blood pressures (range 200 to 280 mm Hg) usually occurs and the hypertension persists as long as 4 years at present It is significant that these dogs never develop a malignant phase as judged by retinitis etc

Does such an experimental hypertension exist and is it sustained or transient? Several have denied its existence or stated that elevations of pressure are an emotional product or as reported by Caroline Thomas an increase of cardiac output with excitement We believed the hypertension to be sustained and sought proof The approach was not simple Here are examples of one group of experiments dealing with anesthesia Blood pressures of normal dogs obtained by arterial puncture before and after anesthesia with chloralose showed little change Blood pressures of neurogenic hypertensive dogs were likewise listed before and after anesthesia with chloralose with no significant reduction The pressures of control animals and of neurogenic hypertensive animals were noted before and after ether anesthesia There was some drop but not to the range of normal With sodium amytal there was little change in the normal dogs and little change in the neurogenic hypertensive dogs Now with pentothal sodium a similar response was observed using neurogenic hypertensive renal hypertensive and normal dogs The neurogenic hypertension values were higher than the renal before pentothal sodium but the end pressures under the pentothal anesthesia were the same in both groups and higher than normal

An approach was made to the problem of getting the blood pressure of the normal dog or of the neurogenic hypertensive dog during natural sleep It was thought that if we could obtain blood pressures during natural sleep we might know whether neurogenic hypertension persisted 24 hours a day or just while the animal was awake A device was arranged with two small cuffs to go around an artery The idea was similar to the one presented by Dr Anderson at this Conference One cuff was placed around the femoral and one around the iliac artery the one on the femoral recording pulsations The cuff on the iliac was used as a pressure cuff which at systolic pressure would cut out the femoral pulsations With this system we were able to measure blood pressure Leads from the cuffs were carried subcutaneously to the back of the dog and there led up to manometer and pressure systems

The dogs were made as comfortable as possible in a cage and observed for 48 hours or longer if necessary As the animal ate or fed we were able to take the blood pressure at any time desired Since the iliac and femoral area was denervated there was no pain The dog was unaware that we were taking pressures and many readings were obtained during natural sleep Mean systolic pressure was obtained using a mercury manometer Pulse rate was noted at the time of the pressure reading

During sleep there is a tendency for the pulse rate and the blood pressure to diminish in normotensive dogs The pulse rate may fall markedly In neurogenic hypertensive dogs pressures remain high during sleep although not as high as while eating exercising etc the lowest average blood pressure reading being 140 mm Hg The normal dogs had a blood pressure level around 90 mm during sleep The lowest natural sleep reduction in neurogenic hypertensive animals was thus well above the highest pressure of normal dogs during sleep

Although some neurogenic hypertensive dogs had only moderate reduction of pulse rate during sleep there was one in which there was a reduction of pulse substantially to normal but no reduction of the mean systolic blood pressure as readings were taken during feeding active standing rest and then sleep

Dogs with renal hypertension were also prepared in the same fashion and studied They exhibited a trend like that of the normal and the neurogenic hypertensive dogs and showed a somewhat decreased pressure during sleep

What role does the sympathetic nervous system play in maintaining the blood pressure of the normal animal? A series of more than 40 normal dogs was subjected to complete sympathectomy and followed for 48 months following the operations The blood pressure tends to decrease after sympathectomy down toward 100 during the first several months and then gradually returns to the preoperative level Although there is not a marked reduction there is some Feeling that recovery or return of pressure might be caused by regeneration we did a sympathectomy again by dividing all rami and again got lowering and then a return toward normal

Several years ago sympathectomized dogs were checked before and after operation from the point of view of essential hemodynamics with the then available methods the Fick formula using direct cardiac puncture for cardiac output the Congo Red blood volume dye method and the Oswald viscosimeter Blood volume was on the average not changed, blood viscosity also was not significantly changed but the cardiac output was definitely reduced It was our feeling then that this reduction of cardiac output need be considered as an explanation for the reduction of blood pressure during the first months after sympathectomy However we found that this reduction persisted a year or two after sympathectomy when the blood pressure was again normal We concluded since blood pressure was well maintained under these circumstances that the total peripheral resistance of dogs certainly could not be decreased by any form of total sympathectomy

Microphotographs demonstrated regeneration beginning a month after a total sympathectomy in scar tissue along the site of removal of the nerves We were therefore aware from the beginning that following any surgical intervention time would limit the value of a preparation for chronic studies A sympathectomized animal is no longer totally sympathectomized after a year A degree of functional regeneration of the sympathetic nerves takes place

There is further evidence which we need not go into However, here is one observation pertinent to the problem of hypertension Neurogenic hypertension pressure levels in two dogs were recorded for three or four months Then a total sympathectomy was performed with a reduction of blood pressure again to somewhat below normal At six months the pressure was back to normal at 12 months going up above normal and then as time went on values around 180 to 200 mm Hg were reached Return was not to the preoperative level but this degree of recovery might be explained by regeneration These dogs did not have celiac ganglionectomy

Further experiments demonstrated that only a total sympathectomy will reduce the blood pressure of neurogenic hypertensive dogs Splanchnicectomies from the nipple line down resembling the conventional operation in hypertensive patients today did not reduce neurogenic hypertension If one leaves the splanchnic area

intact and denervates the upper half of the body head, heart lungs etc then similarly lowering of the blood pressure of neurogenic hypertensive dogs does not occur Only when both areas are denervated including the cardiac as well as the splanchnic and the adrenal sympathetic nerves can one obtain reduction of pressure to normal

A simpler type of neurogenic hypertension is that produced by increase of intracranial pressure The response of an animal who had lost his splanchnic area from the middle of the chest on down including the peripheral trunk as well as the splanchnic and chain branches to the adrenals and kidney resembled the elevation of blood pressure which occurred in the normal animal subjected to increased intracranial pressure When the opposite operation was performed with the heart pulmonary cerebral and upper peripheral trunk denervated but with the splanchnic area intact the pressor response was again like the normal Increase of pressure also occurs after a different type of splanchnicectomy the anterior root ramisectomy In marked contrast is the effect of total sympathectomy If you remove entirely the cardiac and the splanchnic area the increase of intracranial pressure produces death without the animal being able to compensate by increase of blood pressure Many more of these studies have been performed from a month after sympathectomy to a year and one half afterward

It might be well to discuss for a moment the clinical results of sympathectomy The final testing of any form of treatment for hypertension is going to depend upon the accuracy with which we can determine results I believe that everyone will agree that follow up studies must be controlled and continued over a period of years and that even then we may have an error of at least 10 percent A 10 percent reduction to normal of hypertensive patients is according to several observers within the range of what might have happened had nothing been done or conventional treatment employed We have summarized what splanchnicectomy for 950 patients produced in the way of results when followed several years and reasonably carefully reported by a variety of authors There was a mortality risk but the significant thing is that there was no reduction of blood pressure in half of the patients as reported and that in only approximately 10 percent did they report a reduction of blood pressure to below 150/100

All splanchnicectomy operations are devised around the Smithwick which is a combination of Addison and Peet The conventional clinical sympathectomy neglects the head neck chest lungs and heart supplied by the upper thoracic ganglia No sympathectomy is a complete sympathectomy unless one takes the stellate ganglion at one end and the celiac and upper lumbar ganglia at the other

With any form of sympathectomy one runs into an error in diagnosis or prediction of the course of the disease which may approach 10 percent For example a young woman was first seen with papilledema hemorrhages and exudates and a high pressure Under medical observation pressure spontaneously returned to normal and retinitis disappeared A year and one-half later there occurred again a rise and return of retinitis At that time we agreed to perform a splanchnicectomy feeling that it was not much of a hypertension She lived four years with normal blood pressure and then died suddenly with recurrence of hypertension Autopsy revealed a small pedunculated tumor in the fourth ventricle so she did not have an ordinary hypertension at all even though eye grounds were classified as Grade IV

A mild case of essential hypertension was treated by splanchnicectomy largely because of episodes of tachycardia The adrenals were explored during operation because of a possibility of adrenal tumor There was only a moderate hypertension before operation and pressures persisted normally five years after splanchnicectomy

When one goes on to the more persistent or difficult hypertensive problems then by and large the effect of splanchnicectomy is not impressive In a group of fifty odd splanchnicectomies we have had but four reductions of blood pressure to near normal values of which we have mentioned one that in retrospect was not primarily a persistent hypertension problem We agree with others that this operation helps the patient but as judged by the effect on blood pressure it is not often effective If one goes the other way around—and this is a simple test of the role of the sympathetic nervous system in clinical hypertension—by taking it all out as Cannon did in the dog results are far better This operation effects a total visceral area denervation splanchnic and thoracic and a total body denervation if desired or usually denervation of head arms trunk and all but the vasoconstrictor pathways to the legs By leaving vasoconstriction in the legs some proprioceptive adjust

[illegible] in the erect posture remains and the patient is [illegible] rather than wrong side up as with the conventional [illegible] which leaves vasoconstriction only to the upper extremities [illegible]

The operation is done transthoracically in two stages first one side and then the other two or three weeks later The technique is about the same that Cannon originally used in the dog The name of the operation is total thoracic and partial to total lumbar paravertebral sympathectomy splanchnicectomy and celiac ganglionectomy

I won t go into the clinical aspects but I will mention briefly a few patients whose blood pressures have been reduced to normal over a period of years by this procedure because it indicates to us that somewhere in the hypertensive process the sympathetic nervous system must be important They are rather carefully controlled usually with years of observation before and a regular follow up system after operation The patients are readmitted at 3 months and subsequently every year These examples include a Grade IV patient who had had a stroke with marked reduction of pressure after operation Another patient with 3 kidneys had had a progressive increase of pressure before operation and is now living 9 years afterward and still normotensive A boy of 20 with very high pressure was treated with thiocyanate Nine months later the pressure was 240 with a diastolic of 160 at rest in the hospital His blood pressure has been normal for 4 years since operation Another case shows reduction of pressure but not to normal On the whole this is a more frequent result A definite reduction of 60 mm or more in the systolic and 20 mm or more diasstolic occurred postoperatively Although the postoperative pressures were still above normal nevertheless there seemed to be a benefit on the disease process with an arrest of the upward trend of pressures which had been evident before near total sympathectomy Often enough the result is what we call a failure in that there is no reduction or so little that the blood pressure is essentially as high as it was before With these patients also the upward trend of pressure ceases and the residual pressure continues at a plateau year after year By and large the test of sympathectomy was made on seriously ill patients with advanced stages of the disease Relief of symptoms disappearance of retinitis absence of recurrence of hemiplegia etc has been most encouraging

All patients have postural hypotension after near total sympathectomy even those with failure of reduction of supine pressure They lack the proprioceptive adjustment mechanism of the sympathetic system and have a definite reduction of pressure during exercise or in the erect position For example in one patient the blood pressure a year after near total sympathectomy was as high as before (260/140 lying) yet during exercise on master steps it came down to near normal without causing noticeable disability

Does the sympathetic nervous system have anything to do in the long run with ordinary essential hypertension? The individual case studies illustrating effect of complete removal indicate that perhaps it does Also analysis of a group of 113 patients who have now been followed 1½ to 9½ years or on the average 3½ years indicates that removal of the sympathetic nerves alters the course of the disease Of these at the present time the blood pressure remains reduced to near normal in 31 It remains reduced but not to normal in 43 and there was no definite reduction in the supine position in 23 The survival rates are very encouraging Of the original 113 generally severely ill hypertensive patients we now have 97 still living and generally normally active without restrictions or diet or medicine

Now we will turn to the sympatholytic drugs and what they might accomplish We hoped to duplicate the effects of sympathectomy with these so called adrenolytic or sympatholytic drugs I want to mention right now a by product of our studies and admit that it is the only significant product we have had Treatment with Priscoline protects against the vascular spasms and the color changes of fingers in Raynaud s disease

Testing of patients with hypertension using the sympatholytic drugs is apparently no better than testing by any other method according to our experiments As far as I know the reduction of blood pressure obtained from spinal anesthesia through sodium amytal and through tetraethyl has not stood up when carefully analyzed as a prediction of the results of sympathectomy It is my opinion that we are not going to be able to predict the effect of chronic denervation of the vascular bed by any acute test lasting but a few hours Perhaps if we had a drug which could effect a medical sympathectomy for a month or more the chronic

effect on blood pressure might be of value I don t believe that these brief testing periods preoperatively are going to tell us much

This brings us to the problem of the effects of the sympatholytic drugs upon the autonomic nervous system and of chronic treatment in experimental and clinical hypertension A variety of drugs has been studied some of them are described as acting centrally and some of them are ganglionic blocking agents with marked sympathetic and parasympathetic blocking effects The so called adrenolytic or sympatholytic agents are variously effective in stopping sympathetic actions although all have adrenolytic effects In addition to blocking adrenergic conduction some have miscellaneous side actions

A method of testing these drugs on dogs has been devised

The carotid sinus reflex can be produced by putting an inverted vein sac in the sinus and increasing pressure within it by putting saline under pressure into the sinus with ligatures above and below or simply by clamping the carotid artery and thus reducing pressure in pressor sensitive areas and increasing the stimulus through the sinus nerves to the vasomotor center to raise the pressure Cardio aortic stimuli are usually eliminated in experiments in dogs by division of the two cervical vagus trunks

One obtains a rather consistently repetitive type of carotid sinus reflex blood pressure curve If a total sympathectomy is performed and tests are made before regeneration one abolishes this reflex Sympathectomy evidently interrupts all efferent pathways responsible for the reflex Three years later after regeneration the reflex returns and is moderately active

Another method used in the drug testing in animals is stimulation of the central end of a divided vagus nerve This produces a marked pressor response It is an acute reflex and is also blocked by total sympathectomy A few years after total sympathectomy central vagus stimulation produces a slower or humoral type of increase of pressure

Still another method used in the testing is one that will intrigue those of you interested in peripheral resistance It is the method devised by Professor Nolfe of Brussels It does not measure peripheral resistance in units but it does measure the back

pressure in the peripheral ends of divided femoral arteries and probably indicates directional changes of resistance The pressure depends upon collateral circulation around the divided femoral arteries and upon the resistance offered by the smaller vessels located peripherally in the leg In other words the pressure in the distal end of the femoral artery depends upon the blood getting to it and the resistance beyond it It is somewhat complex but does yield a simple indication of changes of resistance It certainly tells what the back pressure in the divided femoral is under varying conditions

During an acute experiment the systemic blood pressure and the left and the right leg back pressures are recorded the latter pressures being fairly substantial The back pressure responds actively or reflexively with changes of systemic pressure occurring with decrease of carotid sinus pressure and with central vagus stimulation When a limb is chronically or acutely denervated then a passive response occurs slowly after and along with changes of systemic pressure Presence or absence of active or reflex responses will test sympathectomy Again a sympathectomized limb responds passively pressure changes following blood pressure elevation

Of the 20 or more drugs tested the most interesting studies dealt with Priscoline C 7337 tetraethyl ammonium bromide and SC 1950

Under chloralose anesthesia and after standard preparation various observations were made in dogs These are the changes of respiration systemic pressure and back pressure in a normal and a sympathectomized leg occurring with peripheral vagus stimulation a check for any atropine like effect injection of epinephrine in small dosage carotid sinus reflex central vagus stimulation and anoxia After control observations the drug to be tested was given and the above observations repeated In a normal response after the drug reflexes remain as before

When an adrenolytic or sympatholytic drug is used various interesting phenomena occur One leg has been denervated and the other is normal Before the drug the blood pressure rise with the carotid sinus reflex is active or prompt in the innervated leg and passive or slow in the denervated limb When one introduces a small dose of epinephrine before the test drug there is a slight

reduction of back pressure and then an increase in the innervated leg and a prompt and greater increase in the sympathectomized limb Although diphasic responses with early decrease of back pressure or peripheral resistance occurred often in the innervated limb it never occurred in the sympathectomized limb vasodilatation presumably being effected by some central action of epinephrine Following Priscoline the response in the innervated limb changed becoming passive like that of the surgically sympathectomized leg Changes of back pressure or of systemic pressure occurring with epinephrine the carotid sinus reflex central vagus stimulation etc were blocked

After Priscoline the small standard dose of epinephrine is blocked However when you give a large dose of epinephrine you get a marked reversal or reduction of systemic blood pressure

In an experiment with C 7337, several tests demonstrated block of reflex effects and pressor responses to epinephrine Dibenamide has an early and a late effect The early effect is a gradual reduction of pressure during which the reflexes may be active Later on they are abolished The action of Dibenamide persists 24 hours or longer SC 1703 is a short acting agent primarily having another effect useful for treating peptic ulcer However it does for a while block the reflexes but not epinephrine The major action is reduction of volume and acidity of gastric secretions and reduction of gastric contractions delaying emptying of the stomach Barium is retained much longer than in the controls

Experiments were done using another group of drugs with different vasomotor effects the ganglionic blocking agents After Etamon or tetraethyl ammonium chloride all of the general vasomotor reflexes are blocked but the response to epinephrine is good since it acts on the end organ and the block is central in the ganglion The drug does not block adrenalin and may even accentuate its action We found following Etamon that vasomotor blocking effects can be antidoted by prostigmine to the point that they will return toward normal

An experiment with another ganglionic blocking agent SC 1950, illustrates the same effects The drug does not alter the response to epinephrine but produces the block of reflexes This drug is equally as effective as Etamon in producing ganglionic block Its side effects on the intestinal tract have been studied in

a patient with a four channel tube and four balloons in the digestive tract One balloon was in the stomach one in the duodenum one in the proximal jejunum and the fourth in the ileum The drug causes cessation of activity at all levels This also is true with Etamon After either drug recovery occurs in a peculiar order in the stomach first then duodenum distal jejunum and finally in the ileum

There is one other method of testing these drugs for their efficiency in generally blocking vasomotor activity They may be used against the increase of systemic pressure occurring with increased intracranial pressure A trochar is driven through the skull and saline injected under pressure The volume is measured so that it will not leak into the cerebrospinal system or into the blood stream A normal response consists of a blood pressure rise to 280 mm Hg

Since the drugs to be tested do reduce blood pressure one immediate problem was can increased intracranial pressure be reduced in animals by ordinary shock? If shock has been produced by the drug it could effect the results An animal was tested before hemorrhage blood pressure and reflexes were noted then after repeated hemorrhages over a period of three quarters of an hour it was tested again The blood pressure was reduced and reflexes were blocked However following hemorrhage and shock increase of the intracranial pressure produced a large increase of systemic pressure Also employed was histamine shock which lowered the systemic pressure and blocked reflexes but again did not prevent a good pressor response with increased intracranial pressure

We checked the response to increased intracranial pressure against the sympatholytic drugs feeling that this test produced one of the most potent emergency vasopressor responses and knowing that it was blocked by total sympathectomy although not by splanchnicectomy Priscoline 15 mg per kg reduced or entirely prevented increase of blood pressure with increased intracranial pressure With Dibenamide there was little increase practically nothing C 7337 completely abolished the increase of blood pressure in three experiments

The ganglionic blocking drugs have a less potent effect Following Etamon or SC 1950 there is a break through and blood

pressure rises We know that these drugs are not adrenolytic and have therefore controlled the experiment by removing the adrenal glands before performing increased intracranial pressure We still get the same degree of pressor response so there seems to be a break through of vasoconstrictor pathways after ganglionic blocking agents

Ganglionic blocking agents have an atropine like effect blocking stimulation of the peripheral vagus they may slow the pulse and they accentuate response to epinephrine Block of reflexes is reversed by neostigmine They do not prevent the hypertension occurring with increased intracranial pressure Adrenolytic or sympatholytic drugs on the other hand do not block the stimulation *of the peripheral vagus having no atropine like effect do block* reflexes and epinephrine are not affected by neostigmine do prevent increased intracranial pressure but tend to produce tachycardia Let me defer discussion of tachycardia to the end It is the biggest limiting factor to use of these agents clinically

What about the effect of these drugs on the blood pressure of unanesthetized normal dogs? The ganglionic blocking agents the centrally acting agents and the typical adrenolytic or sympatholytic drugs usually produce some reduction of the blood pressure of the normal dog Pulse rate increased a little or sometimes did not change

The drugs were tested against neurogenic hypertensive animals Carotid sinuses and buffer nerves had been eliminated months before and their blood pressures were chronically high Several dogs were used for each drug and the numbers showing reduction of pressure were as follows C 7337 reduced 14 of 14 Priscoline 13 of 32 Dibenamine 3 of 4 Etamon 5 of 7 SC 1950 11 of 11 and C 5968 11 of 11 It is evident that many drugs reduce blood pressure toward normal values Of this group of agents the centrally acting one C 5968 and the adrenolytic C 7337 seemed best

To summarize our experiments on drugs that block the carotid sinus reflex and reduce neurogenic hypertension Among the sympatholytic drugs we have extensively tested seven Using the ganglionic blocking agent we have tested two Using certain miscellaneous vasodilators there have been four Six drugs reduce the pressor response of acute increased intracranial pressure but

the ganglionic blocking drugs are relatively the least effective It is evident that many drugs reduce experimental chronic neurogenic hypertension

The clinical trial of these drugs will now be summarized We have been able to demonstrate I believe that certain sympatholytic effects can be achieved and maintained The effects of four drugs Priscoline C 7337 SC 1950, and C 5968 on blood pressure of hypertensive patients was studied with large doses given intravenously during tests lasting four to six hours In some patients these doses do not reduce the blood pressure much there being little variation whereas in others reduction is to normal With Priscoline in 16 hypertensive patients (3 to 4 mg /kg ) reduced blood pressure to normal in 10 C 7337 (1 to 2 mg /kg ) reduced pressure in 6 of 7 SC 1950 (1 5 to 2 mg /kg ) in 7 of 7 and C 5968 (0 5 to 2 mg /kg ) in 7 of 7 patients Doses used were sympatholytic These doses cannot be maintained day in and day out but can be given at single times Postural hypotension occurs with standing after these four drugs

That these large doses are sympatholytic is evidenced in part by skin temperature gradient studies The great toe normally is several degrees colder than the skin of the abdomen This gradient can be abolished usually by surgical sympathectomy the toe temperature being brought up to equal that of the body This elimination of gradient or warming of the toes can usually be effected by most of the drugs tested The cold pressor test and the breath holding test are used as methods of elevating the blood pressure Before Priscoline each test effectively increased pressures in 17 of 20 patients After 100 mg /kg the response was reduced in 5 and abolished in 5 of 10 who were tested with this dose The whole group was tested with a larger dose (150 to 200 mg /kg ) Response to the cold pressor test was reduced in 2 abolished in 12 and actually reversed in 3 Similarly response of breath holding was reversed in 1 reduced in 3 and abolished in 13

These experiments with Priscoline are of interest since we have denervated hearts following sympathectomy for hypertension Tachycardia occurs after the drug in normal patients but not in patients with denervated hearts Therefore we have a *feeling that* the tachycardia is reflex in origin and not caused by a direct drug action on the heart

We have given these four drugs chronically for several weeks or months to enough patients with hypertension to realize about what results can be obtained Reduction of pressure obtained in acute tests cannot be maintained In other words we have a nice treatment for an hour or two for many patients with hypertension or a means to produce hypotension in normal patients but have not yet discovered a drug which can be maintained at sympatholytic or even adrenolytic levels more than a few hours Because of tachycardia and other side effects chronic treatment must be limited to one half or less of the desired amount Pulse rate increased with all adrenolytics used and was variable only with the ganglionic blocking agents

Priscoline has a peripheral or histamine like effect in denervated pedicle skin tubes Such action has not been evident with the other drugs A patient with a peculiar Raynaud s like disease of the tongue was treated effectively by either Priscoline or C 7337

One of the most interesting applications of the adrenolytic drugs would be use in diagnosis and treatment of pheochromocytoma A tumor of this kind was diagnosed using benzodioxane which produced moderate reduction of blood pressure for 15 minutes Treatment with C 7337 produced a normal blood pressure which was maintained essentially throughout operation by repeated injections of 1/6 mg /kg C 7337 intravenously The patient had a smooth course through operation and afterward without having paroxysms of hypertension or the subsequent blood pressure depression which ordinarily accompanies surgery for adrenal tumors

In conclusion we have felt that there is experimental evidence that adrenolytic and sympatholytic drugs do exist We have found by using these drugs in patients that in chronic treatment dosage must be limited because of tachycardia and other side effects It was not possible to administer chronically doses that were adrenolytic and certainly not those which are completely sympatholytic Probably because of this limitation we have not been able consistently to effect reduction of blood pressure over a period of weeks or months in a significant number of patients We hope that perhaps by some combination of drugs or with some new preparation it may be possible to prevent the reflex tachycardia If so it is probable that dosage of some of these agents could be increased chronically to adrenolytic or sympatholytic amounts

*DISCUSSION*

*Goldblatt* This is a good illustration of the importance of limiting each session to a single topic I am delighted that Dr Grimson went right through with his presentation It gives us a chance to ask him a few questions

*Schroeder* This whole subject of adrenolytic agents is some what confused now because of the finding which has come to light recently that epinephrine is not a pure substance

At the Federated Societies it was brought out that in a case of pheochromocytoma 1 arterenol as well as epinephrine was present In the British literature there are two recent references to the fact that in pheochromocytomata there are both epinephrine and 1 arterenol Luduena said that various standard samples of epinephrine which are on the market in this country contain from 12 15 percent or more of 1 arterenol The implications of that finding would be comical if they were not tragic

I wonder whether you have used 1 arterenol as a test sub stance in an attempt to find a true arterenolytic agent

*Grimson* All we have used is what was in the bottle which is labeled epinephrine You are correct in stating that this might contain several things We have not used the pure arterenol or the pure epinephrine

*Wakerlin* I should like to point out that Dr W G Moss in my laboratory has confirmed the facts reported by Dr Grimson in regard to the chronic neurogenic hypertension produced in dogs by debuffering He used essentially the same technique that Dr Grimson used We have neurogenic hypertensive dogs that have been hypertensive for three or four years and are convinced that there is such a thing as neurogenic hypertension It all depends upon the technique of sectioning the vagus in the neck Dr Moss has confirmed the result on the neurogenic dogs in regard to the action of dibenamine We have found the same thing with T E A The blood pressure came down but not quite as low as you have indicated

We have evidence that there may be a renal mechanism acting partly to maintain neurogenic hypertension Giving purified hog

renin (75 units per mg of nitrogen) daily and intramuscularly in a dose of 3 to 10 units per kg of body weight over a period of several months to one neurogenic dog caused a significant decrease in blood pressure This finding suggests that a renal mechanism may be *partially* responsible for the hypertension

I should like to ask whether there is any amount of disturbance in heat tolerance in these completely sympathectomized patients of yours Dr Grimson

*Grimson* The point with regard to renal hypertension is well taken Our earliest studies failed to reveal evidence of this They were based on cord sections If the cervical spinal cord is sectioned in a normal dog blood pressure goes down to about 70 If you acutely section the spinal cord of a renal hypertensive dog it goes down a little but not much If you section the cord of a neurogenic hypertensive dog after months or years pressure goes down to 70 These are crude experiments but would indicate that humoral substances if circulating are not able to maintain pressure as in the renal hypertensive dog It would be very intriguing if there was an overlap between neurogenic and renal hypertension

There is no evidence or complaint by patients of intolerance to heat after near total sympathectomy As cholinergic fibers regenerate most patients have definite areas of sweating and their complaint is excessive sweating in these patches

*Wakerlin* Mr E A Ohler in my laboratory has found that paredrine orally administered causes a reduction in chronic experimental renal hypertension in all the dogs tested It causes an even better reduction to practically normotension in neurogenic hypertensive dogs This also suggests that there may be some interrelation between experimental renal hypertension and neurogenic hypertension Unfortunately we don t know the mechanism of the antihypertensive action of paredrine

*Goldblatt* Would you say you got a reduction to normal with that? Does the effect persist or is it just an immediate effect?

*Wakerlin* A chronic experiment in which we administer the paredrine usually in a dose of 1 mg per kg body weight orally daily The effect sets in about the third week and persists during the period of administration of the drug which may be anywhere from four to six months or longer Mr Ohler has found that the

pressure gradually climbs back up to the original hypertensive level over a period of six to eight or even more months

*Goldblatt* Despite the administration of the drug?

*Wakerlin* After the administration has been stopped That is true both of the neurogenic and experimental renal hypertensive dog

*Katz* You have not tried it on man?

*Wakerlin* No But one investigator in Memphis has tried it in a group of four hypertensive human patients (presumably with essential hypertension) and found no significant change in blood pressure using doses at least as large as ours I don t think this was an adequate test Also I think it is a rather dangerous thing to do I believe we ought to follow through and see if we can find an amine structurally related to paredrine preferably without pressor effect which has the antihypertensive effect That is what Mr Ohler has been looking for and has now tested 12 or more compounds without finding any compound with anything like the effect of paredrine

I would like to point out that Mr Ohler has shown that a tolerance to the pressor action of paredrine develops in the dogs so after a period of several weeks of administration one no longer gets acute pressor effects from the oral or intravenous administration of paredrine but there is that period in the beginning where you do get a definite acute pressor effect Tolerance has also been found to develop in humans

*Goldblatt* When you say the antihypertensive effect do you have any idea where it acts?

*Wakerlin* We have no idea at the present time what the mechanism of action is Mr Ohler started the work on the basis that possibly pressor amines were coming out of the kidneys and that possibly by administering the paredrine the amine oxidase and phenol oxidase activity of the tissues might be enhanced with not only increased destruction of the pressor amine administered but also the hypothetical pressor amines coming from the kidney

*Grollman* I would like to ask Dr Grimson if he will comment on certain observations which we have made on hypertensive dogs and which lead me to believe that there is a fundamental difference

between neurogenic and so called renal hypertension I take it that Dr Grimson believes that human hypertension resembles neurogenic hypertension as produced in the dog rather than renal hypertension In the first place our dogs with neurogenic hypertension survive for long periods whereas the dogs with renal hypertension follow a general downhill course very much like most human patients and at autopsy in the latter we find lesions comparable to those described by pathologists for the human The rise in pressure, particularly the acuteness with which it rises, as Dr Grimson has shown is certainly different in the two Finally one very striking difference is the reaction to exercise in the hypertensive dog One observes a drop in blood pressure in the dog with neurogenic hypertension It seems to me that these very fundamental differences would indicate they are due to two separate phenomena

*Grimson* I think they are separate We have tested it to this extent protecting the kidney by denervation in no way alters neurogenic hypertension When reversed and nerves to the kidney alone are left we could produce a little degree of some sort of hypertension by removing the buffer nerves and producing vasoconstriction of the kidney alone

Many would say that the relative well being of these neurogenic dogs year after year does resemble the course of many hypertensive patients even though the rapid downhill course of the renal dog does resemble that of the less numerous patients who die rapidly of malignant hypertension and renal failure

One comment the renal hypertensive dog dying in the malignant phase *does not have vascular damage resembling the classical* picture of the patient does it? The patient often has a marked degree of arteriolar sclerosis The vascular change in the renal dog is a necrotizing arteriolar lesion without arteriolar sclerosis is it not?

*Goldblatt* I believe and we have published that the lesions which we see in experimental renal hypertension in what we have referred to as the malignant phase are similar to the malignant lesions of human hypertension but in both this lesion is not arteriosclerotic A patient with malignant hypertension however may also have arteriosclerotic lesions where as the dog with hypertension does not He develops a lesion which should never be

referred to as arteriosclerosis This is erroneous It is a degenerative necrotizing lesion, especially of the arteriolar system with or without perivascular inflammation and hemorrhage It is not arteriolosclerosis That should be kept in mind

The dog with benign hypertension in my experience Dr Grollman never develops arteriolar necrosis or sclerosis

*Schroeder* I have an important question Dr Grimson did say in his talk that there were certain vascular changes by which I assumed he meant arteriolar nephrosclerosis in these long standing chronic neurogenic hypertensive dogs Is that true?

*Grimson* Dr Goldblatt was one of the four pathologists to whom specimens were sent from various tissues in dogs after three years of chronic neurogenic hypertension I think he was one of two of them who said there was no evidence of arteriosclerosis The others said it was present listing the degree as 2 to 3 plus Results may have been equivocal because of the method of fixation We don t know It is for this reason that we are trying to produce hypertension in the rat We can more easily outlive his life span and might see what happens later in the course of the disturbance or hypertension

*Schroeder* The literature is equally confused There is one report in which there were vascular changes and one in which there was none

*Wakerlin* We can confirm your remarks on malignant hypertension experimentally produced in the dog The characteristic lesion is arteriolar necrosis We have had benign hypertensive dogs that have come to autopsy after six years of hypertension with little or no arteriolo or arteriosclerosis

*Grimson* A neurogenic dog has never to my knowledge developed a malignant or necrotizing process We would like to try other animals

*Goldblatt* That last point Dr Grimson made is very important if we could only satisfy ourselves that neurogenic hypertension is really a persistent type of hypertension I have not satisfied myself that it is on the basis of a study of our own animals and some that were sent to me by Drs Bing and Thomas of Johns Hopkins and by Dr Grimson It is a strange thing but most of these animals which had registered high blood pressure before

they reached us had blood pressures within normal limits when the determinations were made under our conditions Yet in such animals when they were excited very high blood pressures were recorded by us too I am inclined to think that these animals are only *intermittently hypertensive* especially when excited

*Ogden* In those instances where you took these animals if I can so express it you persuaded them into a state where you got the normal

*Goldblatt* Yes the laying on of hands as it were

*Ogden* Do you recall what the pulse rate was?

*Goldblatt* I do not remember My impression is rapid when the blood pressure was elevated

*Ogden* We have been in the habit of using the pulse rate in the dog as an indicator to tell whether the dog is in a reasonably *calm state or not The figures which Grimson just put up we would* have regarded by our criteria as indicating that the dogs were in a state of excitement It may be that that is actually a fact or it may be a matter of our dogs being chronically depressed by the temperature difference

*Grimson* Whether or not neurogenic hypertension is persistent is tremendously important This is the reason that the experiments described using several types of anesthesia were performed Pulse rates were recorded frequently during each of these experiments as during the tests of natural sleep and activity I want to caution that these dogs lack the normal cardiac rate regulatory mechanism and their hearts can be accelerated easily Also epinephrine can circulate easily If asleep with the pulse rate normal and we have accomplished that in some circumstances you still have a degree of hypertension comparable to renal hypertension This has been checked I think by some others It would be well to caution that if the elimination of the buffer nerves is not complete an excitement hypertension only will result

As indicated by Dr Goldblatt s comments we have had bad luck We went down to Augusta and operated on five dogs for Dr Hamilton The next day the gas line broke and they all died Dr Goldblatt received two dogs We carried them from Chicago to Cleveland and the best one died a day after transfer to his laboratory Dr Hamilton operated on several and it did not work

However in the last few months he has reported success I tried for Irvine Page and obtained I believe two out of 4 persistent Pemember that there is a type of neurogenic hypertension produced by inadequate denervation of buffer nerves which is labile and which comes down when you put the dog to rest It is an incomplete denervation and we discard such animals When operation is complete the results described in the paper will hold We are lucky if we get two persistent hypertensions out of five even with experience It is difficult to get the last of the depressor nerves Would you comment on that?

*Page* You sent us two denervated dogs a number of years ago which were hypertensive and have been so We kept them for 2½ years The dogs were still hypertensive when we finally sacrificed them About three weeks ago we operated on four dogs in Cleveland Two of them are hypertensive and two are not In the past six months our average success in producing hypertension has risen to about 65 percent thanks to Dr Grimson s demonstration of his technique

*Wakerlin* What were your clearance studies on those dogs?

*Page* Normal which indicates increased resistance since arterial pressure has risen

*Schroeder* We can confirm Dr Wakerlin s experiences in neurogenic hypertension Sometimes one must denervate a second time depending on how one cuts the left vagus nerve It is a difficult matter to carry out precisely and sometimes the hypertension disappears Under anesthesia these dogs have elevated blood pressures and increased peripheral resistance in the splanchnic area as measured by our direct method of the falling gradient I am quite convinced now that these are chronic neurogenic hypertensive dogs that cannot be brought down to normal

*Page* I have anesthetized the two dogs that you did for me with pentobarbital and their pressures under deep anesthesia were running around 240 and 230 mm Hg so the pentobarbital certainly did not lower the pressure

*Schroeder* We have about 16 such animals

*Page* I would like to comment on the adrenaline problem I think for the record we should recognize that Peter Holst was the first one to find nor adrenaline in the adrenal gland and U S v

Euler the first to demonstrate it in nerves Goldenburg in this country and Hatten and West in England have added much to our knowledge of nor adrenaline and I think the mechanism of the action of these blocking agents is extremely interesting and it puzzled us for a long time why tetraethyl ammonium which seemed to be the ideal chemical from the point of view of blocking autonomic transmission has a multiple effect The amount of fall in pressure you get depends upon the dosage The first dose gives a fall in blood pressure With the next dose you get less of a fall and after the third or fourth dose you get a pure rise in blood pressure Our findings have been in essence that if you remove the liver no rise in pressure is obtained with T E A If you block with dibenamine or Priscoline and benzodioxane to the extent of inhibiting nor adrenaline you get no response to T E A It seems that it fails as a pure chemical sympathectomy and for selection of patients for sympathectomy because it has multiple action one the reduction in pressure as the result of autonomic blockade *and two the counteraction on the part of the body by liberation* of nor adrenaline which tends to raise the blood pressure

*Kety* Are there any studies to indicate in neurogenic hyper tension that there is a generalized vasoconstriction throughout the body so that the blood flow in every vascular bed is essentially un changed?

*Grimson* So far as I know there are few The one made by Page the kidney maintaining normal flow at a pressure of 250 might indicate that there is a high resistance in the kidney Also the comment by Schroeder would indicate that this holds true for the splanchnic bed

*Bradley* Didn t Dr Bing s dogs have a higher blood flow through the paw ?

*Grimson* I am not aware of those findings

*Lamport* If I understood correctly didn t you have a de creased cardiac output in some of your dogs?

*Grimson* Yes but only in the total sympathectomies in nor mal dogs Neurogenic hypertensive dogs were not tested The normal dog has a decreased cardiac output after total sympathec tomy *In the totally sympathectomized hypertensive patients there* is also a moderate decrease In the hypertensive patients the re

sults which Hickam had at Duke and the earlier studies by Wright Adams in Chicago indicated outputs within the lower range of normal Patients have bradycardia after heart denervation with this near total sympathectomy After total sympathectomy in patients the blood volume and blood viscosity is normal The totally sympathectomized dog also has a normal blood volume and blood viscosity It is interesting that the cardiac output is low normal in sympathectomized hypertensive patients whether the blood pressure is reduced by operation or not

*Goldblatt* I regret that I am obliged to terminate the discussion although I too am much interested in this subject

The next and final item is Dr Kety s presentation of the cerebral blood flow during cardiovascular stress

# THE RESPONSE OF THE CEREBRAL BLOOD FLOW IN MAN TO CARDIOVASCULAR STRESS

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In the past five years since the development of the nitrous oxide technique my colleagues and I have been able to study a number of clinical conditions which have as the common denominator a certain amount of cardiovascular stress I should like to present some of these studies for discussion this afternoon with a special emphasis upon essential hypertension and the effects on the cerebral circulation of an acute reduction in the blood pressure of hypertensive patients The method which we have employed is the nitrous oxide method (2) (5) and since much of what I have to say is based upon results achieved by it in fairness to this group I might mention briefly what that is In fairness to myself I would be lax if I did not take advantage of the keen critical analysis which I may be able to get from such a group as this

If a patient is permitted to breathe 15 percent nitrous oxide and blood is taken from the femoral artery and from the internal jugular vein just as it leaves the skull to be analyzed at appropriate intervals for nitrous oxide content and plotted against time one gets a pair of smooth curves the arterial rising rapidly towards a plateau the venous approaching the arterial From these curves and by the application of the Fick principle it is possible to calculate the rate of blood flow through the brain The Fick principle you will recall will be mathematically expressed for nitrous oxide by saying that the quantity of nitrous oxide taken up by the brain ($Q_B$) in any period of time is equal to the quantity of nitrous oxide delivered by the blood to the brain in the same period ($Q_A$) minus the quantity of nitrous oxide which leaves the brain by means of the veins ($Q_V$) The quantity which is brought to the brain in any time by arterial blood ($Q_A$) is equal to the arterial inflow multiplied by the integral of the arterial concentration from zero to that time Similarly the quantity removed in the same time is equal to the venous outflow (which if

you will is equal to the arterial inflow) by the integral of the venous concentration thus the quantity taken up by the brain in a certain time is equal to the product of cerebral blood flow and the integral of the arterial venous nitrous oxide difference from zero to that time On that basis the cerebral blood flow is equal to the quantity taken up by the brain in time $t$ divided by the integral from zero to t of the arterial venous nitrous oxide difference The arterial venous nitrous oxide difference gives us very little trouble It is obtained by taking samples drawing curves and with a planimeter or trigonometrically calculating it In fact Dr Stead has an easier way to get it that is draw the blood continuously from the artery and vein and thus automatically integrate the curves The difficulty has been to calculate the amount of nitrous oxide which the brain has taken up in time $t$ This is the point at which the first approximation enters If this time is long enough the arterial the brain and the venous blood will all be in equilibrium and the venous blood which drains the brain will have a tension of nitrous oxide which will be equal to its tension in the brain The only question is how long does one have to wait until such equilibrium is sufficiently established that the venous tension is then a good approximation to the brain tension? In studies upon dogs in which I could kill the animals after appropriate times and immediately analyze their brains for nitrous oxide I satisfied myself that that period is about 10 minutes In other words within ten minutes the brain is closely enough in equilibrium with the blood which drains it that the venous blood tension of nitrous oxide represents an approximation to the brain tension of nitrous oxide We have other evidence with radioactive krypton studies in human beings in which it was possible to analyze the brain content of radioactive krypton over a period of time We found similarly that ten minutes represented a time in which one could safely say that approximate equilibrium had taken place If such equilibrium is assumed to exist at ten minutes then the venous blood content multiplied by an appropriate partition coefficient would give us the brain content of nitrous oxide That coefficient has been determined in a number of different ways and found to be unity Since that is the case then substituting for the brain content of nitrous oxide the brain content per 100 grams of brain which we can get from the venous blood content per hundred grams of venous blood one can now calculate the cerebral blood flow in terms of cc of blood per 100 grams of brain per minute

There have been a number of other points upon which we have had to satisfy ourselves As far as the theory goes I feel that the theory is practically as sound as that of the Fick principle In its application to the brain and more recently to the coronary flow one has to be sure that the applications of the technique are valid We have had to assure ourselves that right internal or left internal jugular blood represented a fair sample of mixed cerebral venous blood that we have done by taking bilateral blood flows and have found an anatomical error between the right and the left which was not significantly greater than the duplicate error of analyses upon the same side (2) Repeatedly we have had to assure ourselves that the blood in the internal jugular is not contaminated with blood from extra cerebral sources That we have done by working with neurosurgeons doing arteriography, injecting dye (Evans blue) into the external carotid and trying to pick this dye up in the internal jugular From studies like that we have convinced ourselves that the amount of blood originating in the external carotid which ends up in the internal jugular from which we take it is extremely small averaging about 3 percent (9) and therefore we feel that blood from the internal jugular high up at the superior bulb is relatively uncontaminated with blood from the face and other parts of the head

Quite early in the game we turned our attention to essential hypertension (3), prompted perhaps by a current theory at that time that essential hypertension may have an etiology in a primary cerebral ischemia We measured therefore the cerebral blood flow the cerebral metabolic rate in terms of oxygen consumption ($CMR_{O}$ ) the arterial venous oxygen difference and what we have called the CVR or cerebrovascular resistance That represents an approximation We have determined the mean femoral blood pressure We do not know what it is in the carotid when it enters the brain but we assume that the difference would be fairly constant *in individuals and would be relatively insignificant* Furthermore we have neglected the internal jugular pressure which we have measured in many patients and have found to be relatively negligible compared to the arterial pressure and not significantly different in hypertension from what it is in the normal Therefore by dividing mean femoral blood pressure (instead of carotid minus internal jugular) by the cerebral blood flow we feel a sufficiently reasonable approximation has been made to give us an idea of the impedance that the blood suffers in its passage through

the brain The units are mm of mercury per cc of blood flow per 100 grams of brain per minute The interesting thing in the series of hypertensives—and this series of essential hypertensive patients has been extended now to about 50 with no change whatever in the findings—is that the cerebral blood flow is identical in essential hypertension to what one finds in normal healthy young men Table XXIII The cerebral metabolism is not significantly

TABLE XXIII

CONDITIONS INVOLVING INCREASED CEREBROVASCULAR RESISTANCE

| | MABP | CBF | CVR | $CMR_O$ | $V_O$ |
|---|---|---|---|---|---|
| Normal young men | 86 | 54 | 1 6 | 3 3 | 12 |
| High intracranial pressure | 118 | 34 | 3 5 | 2 8 | 10 |
| Primary polycythemia | 108 | 25 | 4 3 | 3 0 | 11 |
| Cerebral arteriosclerosis | 121 | 41 | 3 0 | 2 8 | 9 |
| Hyperventilation | 98 | 34 | 2 9 | 3 7 | 8 |
| Essential hypertension | 159 | 54 | 3 0 | 3 1 | 11 |

MABP = mean arterial blood pressure (mm Hg)
CBF = cerebral blood flow (cc /100g /min )
CVP = cerebrovascular resistance (mm Hg/cc /100g min )
$CMP_O$ = cerebral oxygen consumption (cc 100g min )
$V_O$ = cerebral venous oxygen content (volume )

different in essential hypertension and since the mean arterial blood pressure is so much higher in patients there is a striking increase in cerebral vascular resistance Looking at the problem *de novo* and without any preconceived ideas we tried to figure out what could possibly cause an increase in the cerebrovascular resistance This approach may seem naive in view of how much work has been done on this increase throughout the body but I feel that if we forget about every other vascular bed that has been studied and confine ourselves to the brain we are not influenced by preconceived notions and second if we happen to arrive at the same answer as have others in other regions both our conclusions are strengthened Three theories occurred to us to explain our results In the first place one may suppose that there is a primary increase in cerebrovascular resistance due to a narrowing in the cerebral vessels followed by a compensatory increase in blood pressure That was the theory which was advanced at the

time we made these studies by Nowak and Walker (8) On the other hand one could say that the hypertension occurred as the result of a mechanism operating entirely outside the brain and that there is within the brain an intrinsic reflex so adjusted as to keep the cerebral blood flow normal This could be the carotid sinus at least that has been suggested in the past In addition to its well known circulatory effects this reflex could also control the innervation of cerebral vessels so that a rise in blood pressure would cause constriction and a drop in pressure relaxation of these vessels to keep the cerebral flow constant at all times in the face of alterations in arterial blood pressure Therefore, such a mechanism might be operating in hypertension It may also be the chemical mechanism for homeostasis in the brain by means of which oxygen and carbon dioxide tensions are preserved and which could not permit a more rapid cerebral blood flow in hypertension than that sufficient to meet the normal metabolic needs and keep a normal internal environment The third possibility was that the increase in cerebrovascular resistance and the increase in blood pressure occurs concurrently just as they occur throughout the rest of the body by virtue of generalized vasoconstriction involving every vascular bed

Perhaps some insight into which of these possibilities we may immediately reject and which we must retain may be gathered by comparison of hypertension with a number of other conditions which we have studied which have in common an increase in cerebral vascular resistance

Going over our data I have chosen a number of clinical conditions in which the cerebral vascular resistance is found to be markedly increased (Table XXIII) The first of these is high intracranial pressure (7) I think the mechanism here is a fairly obvious one In fact when we correlated the cerebrospinal fluid pressure and the cerebrovascular resistance we found a good linear correlation between the two indicating that as intracranial pressure goes up there is increased resistance offered to flow of blood We may even go further and say that the high intracranial pressure causes the increased resistance and that the rise in blood pressure is a secondary and compensatory phenomenon It should be noted that if the cerebrovascular resistance is primary and the blood pressure rise compensatory it is not completely adequate to meet the increased resistance and as a result there is a marked and

statistically significant impairment of the cerebral blood flow. In primary polycythemia we have an obvious mechanism for increased vascular resistance. It is quite high, the highest of any of the group studied, and represents the increased viscosity and the impedance which the blood offers to its flow through the narrow vessels. Here again when the cerebral vascular resistance increases the blood pressure does not rise *pari passu* and again there is restriction in the blood flow. We have studied a number of patients with cerebral arteriosclerosis. These are elderly patients with senile psychosis, presumably on the basis of this cerebral arteriosclerosis. In these patients again there is a high cerebrovascular resistance, probably as a result of the actual organic narrowing of major blood vessels in the brain, with again a rise in blood pressure. This is either compensatory or as the result of arteriosclerosis in other organs in the body. Nevertheless in this situation again the rise in blood pressure does not keep pace with the rise in cerebrovascular resistance and again there is embarrassment of cerebral blood flow. In hyperventilation in normal young men (6) there is an increase in cerebrovascular resistance, presumably due to lowering of the carbon dioxide tension in the brain and a functional spasm or constriction of cerebral vessels. Here again there is a slight rise in blood pressure but the rise in blood pressure does not nearly compensate for the increase in resistance and again there is a quite marked restriction in cerebral blood flow. From all these conditions I think you will agree that essential hypertension is fairly distinct in that although the increase in cerebrovascular resistance is equal to or greater than that observed in any of these other conditions, the increase in blood pressure is quite *adequate* to maintain a perfectly normal cerebral blood flow. On this basis, by comparison with these other conditions in which the mechanism of the increased cerebrovascular resistance is more evident, I think it is fair to conclude that there could not be a primary increase in vascular resistance in essential hypertension with a compensatory increase *in blood pressure*. On that basis one would expect some reduction in cerebral blood flow. Since that is not at all reduced it is difficult to see the stimulating mechanism for the rise in *mean* arterial blood pressure.

I think then that the first possibility, a primary cerebral ischemia, can probably be ruled out of our thinking, which leaves us with the other two possibilities: that the increase *in* cerebral vascular resistance is a response on the part of *the brain to a*

hypertension arising elsewhere or simply a reflection of the generalized constriction that we know occurs in every other vascular bed which has been studied

*Katz* Just a quick question — it is possible that it might be primary in part of the brain say the hypothalamus, without being primary throughout the brain?

*Kety* I certainly would have to agree with you there There could indeed be an ischemia of a small part of the brain which we would not detect in measurements of the overall cerebral circulation

What is the nature of this increased cerebrovascular resistance? What have we learned about it thus far? One of the first things we were able to rule out was the possibility that it might have been mediated by known sympathetic innervation to sympathetic vessels Drs Harmel Hafkenschiel and others of us at the University of Pennsylvania have measured the effect of bilateral stellate ganglion block upon cerebral blood flow and vascular resistance in essential hypertension (1) It was found that bilateral stellate block had no effect on blood flow in normal individuals or in those with essential hypertension It did not produce any lowering of cerebral vascular resistance That does not completely rule out the sympathetic system as a mediator of this high resistance in the brain but it does cast considerable doubt upon it The patients all showed signs of sympathetic paralysis in the face and eyes and other sympathetic pathways to the brain have not yet been described In another effort to gain more insight into the nature of this increased resistance and secondly to answer the practical question of how safe it is to lower the blood pressure of essential hypertensive patients acutely we have tried to study these functions in patients in whom an acute reduction in mean arterial blood pressure could be achieved by a mechanism not directly involving the cerebral vasculature (4) The mechanism I mean is differential thoracolumbar sympathetic block the injection of 0 2 per cent procaine in the lumbar subarachnoid space with resultant block of the sympathetic outflow in the thoracolumbar region without affecting the motor innervation We have studied a series of some 17 patients which I have summarized in Table XXIV In general it was quite easy to produce a marked drop in blood pressure by means of this procedure However this drop in blood pressure showed a definite trough then very quickly rose to a

TABLE XXIV

THE EFFECTS OF THORACOLUMBAR SYMPATHETIC BLOCK IN HYPERTENSIVE PATIENTS

| | Control | During Block |
|---|---|---|
| Mean Arterial Blood Pressure mm Hg | 155 | 115 * |
| Cerebral Blood Flow cc /100g /min | 52 | 46 * |
| Cerebral Oxygen Consumption cc /100g /min | 3 3 | 3 2 |
| Cerebrovascular Resistance mm Hg/cc /100g /min | 3 1 | 2 6 * |
| Cerebral Venous Oxygen Content volume % | 10 6 | 9 5 * |

*Indicates a statistically significant change (p less than 0 01)

plateau which was still below the normal resting pressure in those individuals We studied cerebral blood flows not at the deepest point because with this method we need a period of ten minutes of a relatively steady state To make a valid measurement in this trough which lasted for a very short time we would need a much more rapid technique We have however studied the cerebral blood flow in the relatively long plateau period after the drop in blood pressure

*Wakerlin* You want to indicate the degree to which the level drops on the average?

*Kety* The mean blood pressure starts at 155 mm Patients will vary I don t know what the average trough would be I have seen troughs as low as 80 mm frequently and occasionally 60 mm I do have the average figure at the plateau which is 115 mm of mercury Some patients won t show this trough at all but gradually go down then level off

The values in 17 patients in whom we measured cerebral blood flow and the other functions before and during the sympathetic block are shown in Table XXIV The mean arterial blood pressure falls considerably representing an average drop of about 27 per cent The cerebral blood flow falls also This is statistically significant and represents a drop of about 12 percent The cerebral

oxygen consumption does not change significantly Now it will be noted that although the cerebral blood flow falls when we drop the blood pressure acutely this decrease in cerebral blood flow is not commensurate with the fall in mean arterial blood pressure This can only mean and calculation shows it does mean that the cerebral vascular resistance has relaxed to a significant extent following the acute drop in blood pressure Thus the cerebral blood flow does not fall to as low a figure as would occur were that not the case As the result of the moderate restriction in cerebral blood flow which nevertheless does occur there is a significant fall in venous oxygen content from 10 6 to 9 5 volumes percent We can conclude that the resistance is capable of immediate relaxation in essential hypertension in response to a drop in blood pressure This relaxation is not by any direct effect on cerebral vessels since the thoracolumbar denervation would not have involved the cerebral circulation Furthermore this relaxation which does occur in the cerebral vessels is not complete If it were complete the cerebral blood flow should have been completely maintained

As I said before we did not measure cerebral blood flow in these patients at the point of greatest blood pressure reduction since this state was maintained for only a few moments That was sufficient however to enable us to draw a pair of samples for a cerebral arteriovenous oxygen difference and from this determination we may obtain some indication of what was happening in the cerebral circulation I realize that the arteriovenous oxygen difference has been used frequently and not always appropriately in the past as a measure of blood flow or metabolism and I have been among those who have insisted upon the fallacy of such an application The arteriovenous oxygen difference does however measure something quite validly and that something as one can demonstrate from the Fick principle is the ratio of metabolism to blood flow Another way of putting it is that the arteriovenous oxygen difference is inversely proportional to the blood flow per unit of metabolism This ratio in the case of the brain we may call the cerebral circulatory sufficiency If the cerebral arteriovenous oxygen difference increases we know that cerebral circulatory sufficiency or the cerebral circulation per unit of cerebral metabolism has decreased even though we know nothing of what has happened either to cerebral blood flow or to cerebral oxygen consumption alone

*Cournand* Does that apply to unsteady states?

*Kety* It does unless one postulates the storage of oxygen in the brain At the tensions of oxygen which are known to exist there according to measurements that Davies has made with the oxygen electrode I think there would be very little storing of oxygen in the brain and if no storage occurs the Fick principle must apply

*Cournand* You are speaking of arterial venous difference of oxygen Is that fixed during a period of time or changing?

*Kety* It is constantly changing in a patient like this as you will see the oxygen difference changes quite markedly as one drops the blood pressure but I believe at any instant it certainly represents this ratio of one to the other unless there is a piling up or release of oxygen from the brain itself which with the very low tensions of oxygen which exist in the brain is hardly a very likely possibility The Fick principle has to hold at all times except in so far as a storage or release of a substance in an organ may occur Therefore on this argument—

*Katz* Dr Kety just a moment! It is possible that some blood might be trapped and not be in motion as shown when you do that for the limbs The second thing is that you have a skew in timing You recognize those two You don t think they are important and on that basis you say they give you a measure?

*Kety* The brain is a very peculiar organ It has very little capacity to store blood It cannot store blood very well because of the rigidity of its covering And the time lag is only 2 seconds from artery to jugular vein

*Cournand* I withdraw my comment As long as the absorption is constant you are perfectly correct

*Kety* Even if the oxygen consumption of the brain varies the a v oxygen difference is still a measure of the ratio of blood flow per unit of metabolism regardless of what the metabolism and blood flow themselves separately are doing If you want to go one step further and assume that the metabolism remains constant throughout all these procedures then you have an indirect measure of cerebral blood flow However I have not felt moved to make that further assumption At any rate without making that assumption one can say that the AV oxygen difference if it increases indicates a lessened ability of the cerebral circulation to

circulation We have not tried to raise artificially the blood pressure in man

*Fremont Smith* It is my impression that there is in the literature reference to an experiment with arterial venous aneurysm in man where the spinal pressure was measured while the aneurysm was still present It was possible to produce an abrupt rise in blood pressure experimentally with no change in the spinal fluid pressure I think you will find it in some of Wolff and Forbes observations measuring arteriolar constriction in the meningeal vessels

*Kety* I am not familiar with that particular paper

However interestingly enough if the brain permits an increase in its arterial venous oxygen difference as a result of a sudden drop in blood pressure and therefore probably is permitting a restriction in the circulatory adequacy then this intrinsic neurogenic mechanism which Dr Fremont Smith was just remarking upon could hardly be the sole explanation of the increase in cerebral vascular resistance which exists in essential hypertension because if it were a pure neurogenic reflex one would expect it to respond immediately to a drop in blood pressure This drop is rarely beyond the normal limit If it were simply a compensatory reflex constriction in the face of a high blood pressure when that blood pressure is released one would have to expect a simultaneous release of that constriction and therefore no impairment in the circulatory cerebral competence At least it suggests to me that the neurogenic reflex protective mechanism which certainly exists, can hardly be the sole or the most important part of the increased resistance which occurs in hypertension

The same sort of phenomenon is illustrated if we plot the venous oxygen content against the drop in mean arterial blood pressure, which I have done in Figure 48

Here we have plotted as abscissa the change in mean arterial blood pressure and as ordinate we have plotted the change in the internal jugular oxygen content This is a measure or index of the homeostasis of the brain at least with respect to its ability to maintain a normal oxygen tension I submit that the venous oxygen content is only a rough approximation to the oxygen tension of the brain but certainly the two must vary in fairly parallel direction and if the venous oxygen content drops that must indicate that the brain is actually undergoing a shift towards anoxia On

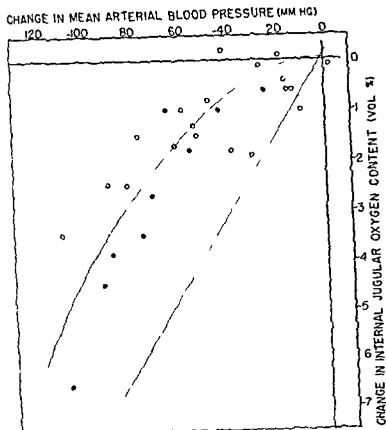



FIGURE 48 Change in internal jugular oxygen content plotted against change in mean arterial blood pressure The horizontal line at 0 change in oxygen content represents perfect cerebral oxygen homeostasis the diagonal line represents the expected line of regression if no cerebrovascular relaxation occurred The curve is the parabola of best fit Solid circles represent those observations made during the occurrence of any symptom referable to the brain

this graph the horizontal line indicating zero change in venous oxygen content would represent perfect oxygen homeostasis for the brain In other words if the cerebral vascular resistance could dilate sufficiently with the drop in blood pressure the venous oxygen saturation or venous oxygen content would never change indicating that the competence of cerebral blood *flow to metabolic* demand would remain unaltered Conversely it is possible to calculate what would have happened in these same patients *if the cere*bral vascular resistance did not alter in any way but remained

perfectly rigid with a drop in blood pressure When one makes this calculation one gets data which form a very good line of regression This line which the calculated data fit with a correlation of 0 95 is the diagonal line in Figure 48 This diagonal represents what would have happened to these patients had there been no compensatory adjustment at all in the vascular resistance Notice that what actually happened to the patients lies somewhere between these two extremes These data form a parabolic curve represented by the parabola of best fit so that there is a reduction in oxygen homeostasis in the brain as the blood pressure falls but this reduction is not as great as it should have been had there been no compensatory vasodilation on the part of the cerebral vessels Here we were able to include data way down the scale whereas before we had to confine it to data with a relatively moderate decrease These two lines of approach both indicate simply that cerebral vascular resistance in hypertension relaxes when the blood pressure is acutely reduced but that this relaxation is not immediately great enough completely to preserve cerebral homeostasis

I forgot to mention the important point that was brought up by Dr Fremont Smith which would now be appropriate You mentioned what was not evident to me until I had studied the data for a long time that is that patients hyperventilate as the result of hyperventilation they decrease their carbon dioxide tension and as the result of the decrease in carbon dioxide tension we know that cerebral vascular resistance could increase Therefore this whole phenomenon could be due to hyperventilation which accompanied a drop in blood pressure and prevented complete relaxation of cerebrovascular resistance We have analyzed these same data with associated carbon dioxide changes with the use of partial coefficients of correlation by which it is possible to rule out the effect of one on the other When we take the carbon dioxide we find that its effect is minimal as contrasted to the drop in blood pressure even though the carbon dioxide change did occur In fact if we treat the parabola of Figure 48 as a linear regression which is a little unfair to the data but we will do simply because parabolic regressions are terribly complicated we get a correlation coefficient of 0 84 If we now treat to eliminate the effect of carbon dioxide changes we get a partial coefficient of correlation of 0 74 and this indicates that the carbon dioxide change which we thought might actually contribute markedly to this is actually hardly responsible for any of the effects observed

*Fremont Smith* May I throw in another challenge with reference to the effect of carbon dioxide? This apparently is chemical rather than neurogenic although it may act on the nerve endings in the cerebral vasculature As far as is known carbon dioxide is the most effective vasodilator of the cerebral vessel H S Forbes and H G Wolff have shown this clearly and also that there is active vasoconstriction of the cerebral arterioles if the animal is hyperventilated This cerebral vasoconstriction with hyperventilation may well account for the fact that patients during examination of the lungs in a sitting position frequently feel faint after the doctor has asked them to take a deep breath repeatedly

Secondly is it possible that your blood being in a state of some degree of alkalosis would shift the carbon dioxide oxygen tension? That is an association which is going to complicate your use of oxygen and carbon dioxide consumption I think you will need a more direct evidence that the immediate and rather profound alkalosis and overventilation and washing out of the carbon dioxide which will take place under those circumstances play no role

*Kety* I agree with you entirely Dr Fremont Smith We have been able to confirm the observations in animals and in man that carbon dioxide is the most potent vasodilator and lack of carbon dioxide is also a most potent vasoconstrictor We can in addition to the statistical studies do some studies while maintaining the carbon dioxide tension in blood constant and that should certainly be done

*Fremont Smith* I would like to emphasize the importance of carbon dioxide in a variety of conditions such as high altitude flying The attention of the workers has been focused upon getting oxygen to people flying at high altitude by increasing the oxygen tension of arterial blood with no consideration whatsoever of the rate of delivery of arterial blood to the brain cells The rate of delivery is greatly affected through Poiseuille s law by the degree of vasodilation or constriction of the arterioles A small amount 10 percent of carbon dioxide and 90 percent oxygen will make the retinal veins in man bright red in about six minutes indicating that the blood flow through the brain is enormously increased Apparently the washing out of carbon dioxide does it Carbon dioxide as a vasodilator should therefore be given careful consideration in that situation too Perhaps aviators should have a little carbon dioxide put in the 100 percent oxygen to keep the cerebral blood vessels open so that the oxygen can get there

*Kety* One further point before I give you data on sympathectomy you may have wondered about what the black dots mean as opposed to the open circles Some of these patients had symptoms which we might have attributed to cerebral ischemia symptoms of weakness nausea vomiting profuse sweating and sometimes syncope Whenever that has occurred we have indicated it by a solid circle It is interesting that 8 of the 9 observations made during symptoms fall below the average response, indicating that those symptoms occurred when the brain suffered its greatest departure from homeostasis

*Shorr* Did you do lactic acids on those?

*Kety* No This can also be confirmed by the average figures for venous oxygen In the patients who had symptoms the average oxygen content was 7 8 volumes percent at the time of the symptoms and in those where no symptoms attended the observation the average venous oxygen content was 9 5 volumes percent I simply offer that as an aside suggesting the perfectly obvious thing that these symptoms may have been the result of cerebral anoxia

*Cournand* I would just like to know whether you have any data on cerebral blood flow in clinical conditions where the carbon dioxide tension in the arterial blood is abnormally elevated and constantly so such as in cases of chronic pulmonary emphysema with anoxia polycythemia and in cardiac failure Most have a large total blood flow and I wonder whether they have a greater cerebral flow

*Kety* I have some observations which we made in association with Julius Comroe in patients with emphysema who maintain a high carbon dioxide tension there is in those patients a rapid cerebral blood flow just as one gets in normal individuals who breathe 10 percent carbon dioxide

*Cournand* Would you express that in quantity?

*Kety* I would merely be able to guess We have done about four or five of these individuals and on the average the cerebral blood flow I should say was close to double the normal

Data obtained in collaboration with Dr Shenkin before and after sympathectomy are interesting and I would like to present them The blood pressure drop in differential spinal was from 155 to 115 mm Hg whereas in the sympathectomy patients it was from

151 to 131 mm Hg The cerebral blood flow values in differential spinal went from 52 to 46 cc per 100 grams per minute while in the sympathectomies they went from 55 to 57 not a significant increase but certainly no decrease The cerebrovascular resistance in the differential spinal group went from 3 1 to 2 6 and in the sympathectomy series it went from 2 8 to 2 3 The oxygen consumption did not change in either series One could derive from this the fact that if the patient is given a long enough time to compensate he is able to relax his cerebrovascular resistance sufficiently to maintain normal cerebral blood flow The only joker is that with sympathectomy blood pressure does not fall as much as with differential spinal block If we were able to drop these down to 115 then we might have found some embarrassment of the cerebral blood flow What suggests itself to me at the moment is that if a large enough series of sympathectomies were built up one could select from that series those patients who show a drop in blood pressure of magnitude similar to that with spinal block and then compare the cerebral blood flows and resistance until that time I suppose there is very little that we can add

In summary there is an increased cerebral vascular resistance in essential hypertension which in contrast to the other types of cerebral vascular resistance increase appears not to restrict the cerebral blood flow and therefore is probably not primary to the hypertension at least throughout the brain This increase in cerebral vascular resistance is not released by bilateral stellate ganglion block However it is released when the mean arterial blood pressure is acutely dropped This release however is not complete and there is therefore a significant restriction in cerebral blood flow Why the release is not complete is still obscure

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*Goldblatt* Gentlemen this has been a profitable experience for all of us The reading of the transactions I am sure will prove even more so Thank you for your active participation in the discussion which has helped to make this Conference a success

*Wakerlin* Mr Chairman I move a vote of thanks to the Josiah Macy Jr Foundation Dr Fremont Smith and Miss Freed for the splendid opportunity offered by this Conference

*Fremont Smith* May we move a vote of thanks to the members of the Conference for making the Conference so successful?

*Goldbtatt* It is unanimously carried